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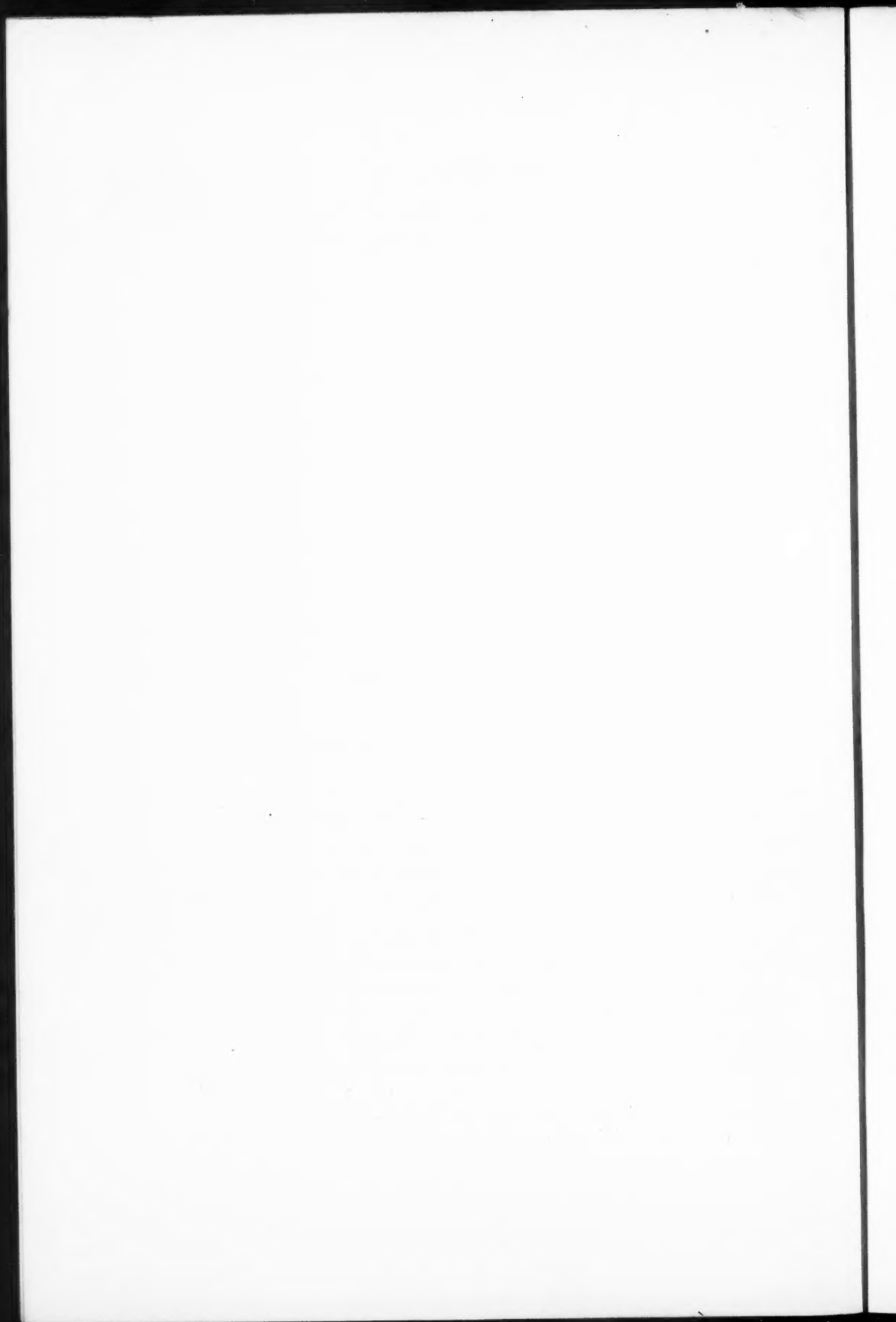
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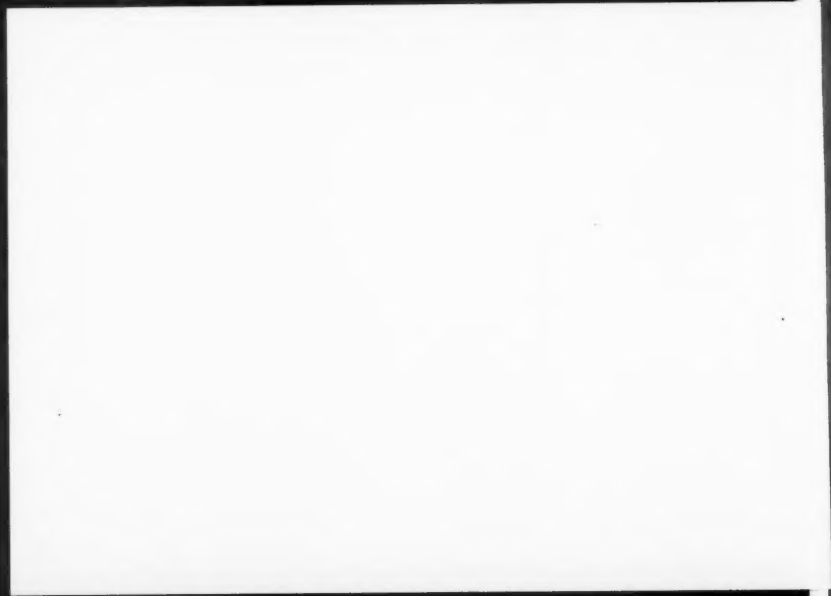
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TUBEROSE SCLEROSIS, RHEOSTOSIS, AND  
NEUROFIBROMATOSIS<sup>1</sup>

By G. S. HALL

(From the Department of Neurology, Birmingham United Hospital)

With Plates 1 to 3

TUBEROSE sclerosis is a disorder in which numerous sclerotic areas of varying size may occur in any part of the cerebrum. The condition is frequently associated with cutaneous lesions and sometimes with tumours of the retina, kidney, heart, spleen, liver, and duodenum. The most characteristic cutaneous lesion is the facial adenoma sebaceum, but fibromata of the skin, shagreen patches, pigmentary and vascular changes, and lipomata also occur. The disorder, therefore, may involve several systems of the body. Lesions of bone, however, appear to be extremely rare, and few instances of their occurrence have been recorded. The purpose of this paper is to consider the nature of these bony lesions, to describe them in two additional cases, and to comment upon certain other rare features which these cases present.

*Case Records*

*Case 1. History.* F. W. P., male, aged 34 years, has had a facial eruption all his life. He was apparently well until 17 years ago, since when he has had increasing bilateral deafness; he has had occasional throbbing noises in both ears since the onset of deafness, but no ear discharge. He has also had infrequent 'black-outs' in which he seems to lose contact with his surroundings, but he has never lost consciousness and has never had a fit. His parents are dead (cause unknown) but, so far as he is aware, neither of them suffered from fits or had a facial eruption. He has three sisters living, all of whom are said to be well.

*Examination.* He is a well-developed man of early middle age, co-operative, well balanced, and of average intelligence. There is an extensive eruption of the Balzar type of adenoma sebaceum covering the whole of the face. There are two large fibromata in the left fronto-temporal region and several smaller ones in the remainder of the scalp. There are many small pedunculated dermal tags on the back of the neck, a few tiny cutaneous and subcutaneous fibromata scattered over the back and thighs, and a more diffuse soft fibroma in the skin of the distal end of the right ring finger on its ventral aspect. In the lumbo-sacral region there is a small shagreen patch, while the skin of the upper part of each thigh is extremely atrophic and wrinkled in places. All the nail-beds of the toes, with the exception of the big and little toes of the right foot, are remarkable for the presence of painless nodular growths of a warty type which vary in size from a pin's head to a

<sup>1</sup> Received August 1, 1939.

structure which in the case of the fifth left toe has almost completely replaced the nail (Plate 1, Fig. 1).

There is an ill-defined elliptical lesion of the retina at about one disk's diameter away from the nasal side of the left papilla. This lesion, which is of a light-greyish colour and is obscured by slight surrounding oedema, is a little raised above the surface of the retina and does not appear to be cystic. It seems to lie behind the main nasal vein and in front of the corresponding artery, which has a tiny aneurysmal swelling on either side of it as it emerges from behind the lower border of the lesion, while there is a tiny haemorrhage about midway between it and the disk.

The deafness is bilateral, severe, and of the inner ear type (Mr. Stirk Adams); the remainder of the physical examination is negative. The serum calcium and phosphorus are 11.1 and 3.3 mg. per 100 c.c. respectively and the serum phosphatase is 4.2 units (28.3-39). X-ray examination of the skull (Plate 1, Fig. 2) reveals the following abnormalities. In the frontal region there are irregular areas of increased density which give a woolly appearance to the affected part. In the parietal region the venous channels are dilated, while there are several small scattered areas of intracranial calcification visible above the sella turcica. The petrous bones (Plate 1, Fig. 3) are unusually dense and massive, while their postero-superior margins are uneven from what appears to be an overgrowth of bone; the internal auditory meati cannot be seen clearly owing to the increased density of the surrounding bone. Each ulna (Plate 2, Fig. 4) is broadened along its whole length, and has a rarefied appearance in its upper third suggestive of a fibro-cystic type of change. All the bones of the hands (Plate 2, Fig. 5) are a little broadened, and several of the phalanges have tiny subperiosteal and cortical areas of rarefaction suggestive of cyst formation.

*Case 2. History.* H. A., male, aged 16 years, came under personal observation in March 1936. He is the oldest of a family of six, all of whom are known to be well and normal, with the exception of the father, who has not been examined. The fourth child, a girl of 7 years, is a twin, whose sister survived birth only for 12 hours. The paternal grandfather died of tuberculosis, but no other details of the family history are known. The patient was born when his parents, who are not consanguineous, were in the early twenties. According to his mother, the pregnancy was normal, but labour, which lasted only 1½ hours, terminated in the birth of a cyanosed baby weighing 7½ lb.; forceps were not used. Development was normal until the age of 7 months, when he began to have fits, which have recurred at irregular intervals. Teething and talking are stated to have commenced at normal times. When he was one year old his mother noticed a rash on his face; this rash, though it has varied in intensity, has slowly become more marked. He began to walk at the age of 16 months, though for 6 months prior to this his mother had noticed that he dragged the left foot when she tried to teach him to stand. At the age of 3 years, when he fell out of his perambulator and sustained a fracture of the right forearm, his mother noticed that the right thumb and forefinger were deformed. When he was 7 years old he fell down a ladder from a height of 20 feet, fracturing his pelvis and right forearm, and was thought to have damaged a kidney because he had haematuria; unfortunately, no notes concerning his admission to hospital on this occasion are available. He began school at the age of 5 and left when he was 13 years old; according to his mother he was dull and did not make good progress. Since leaving school he has had several jobs, from which he

has been discharged on account of forgetfulness or fits. He has always been reliable and good-tempered, and is fond of drawing and playing the piano, though he cannot read music. Since he was 12 years old, he has complained intermittently of headache and of slowly increasing mistiness of vision, particularly of the left eye. He has occasional attacks of vomiting, and his head has increased in size during recent years. Since the age of 14 years, he has complained at times of an aching pain along the whole length of the left leg, particularly around the knee-cap. The fits occur at any time of the day or night, are generalized in nature, and are said to begin more often in the right arm; they are always associated with complete loss of consciousness, and are not followed by any unusual after-effects. His mother is not satisfied that medicines in any way lessen the frequency or the severity of the attacks, which occur as often as several times in one day or as rarely as once every few months.

*Examination.* He is a pleasant co-operative boy, a little undersized for his age, with a facial eruption characteristic of adenoma sebaceum of the Pringle type. His mentality is slightly subnormal. He is quiet and reserved in manner and of a placid disposition; his speech is normal apart from the naïveté of some of his remarks. He has the habit of performing tapping movements with the fingers of either hand when engaged in conversation, and is a confirmed nail biter. The head is rather large, measuring 23 in. round its widest circumference, and gives a 'cracked-pot' note on percussion.

The right hand (Plate 2, Fig. 6) shows the following abnormalities. The proximal half of the thumb is enlarged to form a hard nodular swelling on its ventral aspect, while the forefinger, the skin of which is tense and shiny, is considerably broadened and very nodular: there is limitation of movement of both these digits. The proximal third of the middle finger is a little expanded, while the distal two-thirds are displaced mesially by the increased width of the forefinger; the inner two fingers, particularly the ring finger, are unusually thin and tapering. At the base of the thenar eminence there is a slight thickening of the subcutaneous tissue which appears to be part of a fluctuating and painless swelling involving the sheaths of the flexor tendons. The left hand is normal apart from the tip of the ring finger being missing as the result of an accident, and there is no other obvious abnormality of the skeleton.

*Eye examination (30.3.36):* there is considerable chronic bilateral papilloedema; no haemorrhages are present. There is a small, ill-defined, greyish, and non-pulsatile swelling in the right fundus attached to the upper nasal margin of the optic disk (Plate 3, Fig. 7). The left fundus is somewhat obscured by a vertical lobulated opacity of the upper part of the lens. Apart from a right lower facial weakness, the nervous system is normal. The other systems of the body are also normal. The blood Wassermann reaction is negative.

*X-ray examination.*

1. The skull shows some deepening of the sella turcica, separation of sutures, and the generalized markings of severely raised intracranial pressure.

2. The right hand (Plate 3, Fig. 8) shows marked hyperostosis of the bones of the index finger, thumb, and, to a slight extent, of the proximal phalanx of the middle finger. The phalanges of the index finger, the proximal phalanx of the thumb, and, to a very slight extent, that of the middle finger, show a varying fluffiness of outline on their ventral and lateral aspects due to an overgrowth of the periosteal bone into the adjacent soft tissues. The appearance suggests that the lesion began as a localized overgrowth of the

periosteal bone (as seen on the radial border of the proximal phalanx of the middle finger) and that the whole shaft of the affected bone was eventually involved in the process (as has occurred in the case of the index finger). The first and second metacarpal bones are considerably broadened and, in contrast to the affected phalanges, have a well-defined outline; the second metacarpal is stouter and denser than the first. The only other abnormality present is some irregularity of outline of the terminal phalanx of the thumb on its ventral aspect. The epiphyses of all the affected bones appear to be normal.

3. The lumbo-sacral spine, the feet, and left knee are radiologically normal.

21.10.37. Pulse rate persistently raised (average of 100); electro-cardiogram normal. Occasional trace of albuminuria present. Intense bilateral papilloedema still present. Approaching the extreme temporal periphery of the left fundus there are to be seen two sharply defined whitish-yellow spots, while a larger one is present in the periphery of the lower nasal field (Plate 3, Fig. 9). There are also present two larger, ill-defined circular lesions and what appear to be numerous tiny naevoid areas at the most extreme temporal periphery, where some of the blood vessels acquire a whitish streaky outline. The appearance of the swelling attached to the upper nasal margin of the right disk is unchanged. All tendon jerks are sluggish, and there is an extensor plantar response on the left side. X-ray examination of the right hand does not reveal any further change. The skull possibly shows more marked radiological evidence of raised intracranial pressure, while in the lateral view there are to be seen several tiny scattered spots of calcification. The cerebrospinal fluid has an initial pressure of over 300 m.m. of water, is clear and faintly yellow; its protein content is 1200 mg. per 100 c.c., there is a considerable amount of globulin present, the Lange curve is 3141100000, the cell content is normal, and the Wassermann reaction is negative. The serum calcium and phosphorus are 10.3 and 4.8 mg. per 100 c.c., and the serum phosphatase is 9.8 units (3.11.37).

16.6.38. General condition unchanged. The optic disks are beginning to show definite consecutive optic atrophy. X-ray examination of the right upper limb does not show any further change in the condition of the hand, but there is possibly slight thickening of the humerus just above the elbow joint.

7.3.39. The papilloedema has completely subsided, and the optic atrophy is more apparent. The lower pole of the right kidney is palpable, but there is no albuminuria. The radiological abnormalities are still confined to the right hand, the appearance of which is as it was three years ago, with the exception that the epiphyses are now fused with the bone shafts; the right humerus appears to be normal.

#### *Discussion*

*Bony lesions.* Sailer (1898) recorded thickening of the skull in several of the post-mortem findings which he reviewed, and Lind (1924) recorded a similar finding in one of his cases. Critchley and Earl (1932) stated that it was not usual to find any obvious abnormality either in the cranium or in the meninges in tuberosc sclerosis, although at times both these structures were somewhat thickened and ossification of the sutures was present; they noted the frequency with which such stigmata of degeneration as the simian

hand, shortening and incurving of the little finger, supernumerary digits, hemi-hypertrophy, spina bifida, and cranial anomalies occurred.

Van der Hoeve (1932) referred to the findings of Pincherle and Horniker who described radiological changes in tuberose sclerosis, consisting of osteoporosis and pneumatization of the skull bones, and typical enlargement of the markings of the diploic vessels; he also mentioned a suggestion made by Horniker that there may be a connexion between the cranial defects which occur in this disorder and those of the Hand-Schüller-Christian disease. In considering the 'phakomatoses', as he collectively named tuberose sclerosis, neurofibromatosis, and the true blood-vessel tumours of the brain (the disorder of von Hippel-Lindau), van der Hoeve stated that other affections of bone such as tumours and cysts were also found, and that in some cases there was a connexion with such disorders as Paget's disease of bone and von Recklinghausen's disease of bone.

Unfortunately confusion has arisen concerning van der Hoeve's references to these bony lesions, and subsequent writers (Gottlieb and Lavine, 1935; Dalsgaard-Nielsen, 1935) have stated that Paget's disease of bone, osteitis fibrosa, tumours, and cysts of bone have all been reported in tuberose sclerosis. It would seem, however, that van der Hoeve first referred to the radiological findings of Pincherle and Horniker in tuberose sclerosis, and then indicated that tumours and cysts of bone and changes which resembled or suggested a connexion with osteitis deformans and osteitis fibrosa cystica also occurred in the 'phakomatoses'. Such bony lesions, however, are known to occur in neurofibromatosis, with which tuberose sclerosis is very occasionally associated, and with which it may have genetic associations (Hintz, 1911; Orzechowski and Nowicki, 1912). It is possible that the cranial defects to which Horniker referred were due to neurofibromatosis, while the suggestion by van Wulfften Palthe (1932) that a tumefaction might affect the parathyroid glands and so cause the appearance of osteitis fibrosa cystica was made with reference to this disorder (neurofibromatosis), and not, as Gottlieb and Lavine imply, in connexion with tuberose sclerosis.

Gottlieb and Lavine (1935) published a case of tuberose sclerosis which had peculiar bony lesions limited to the skull, the hands, and the feet. On X-ray examination there was a curious mottling of the skull with indistinct islands of increased density alternating with areas of rarefaction; both the internal and external tables of bone appeared thicker and denser than normal, there were no areas of destruction visible, the sella was normal, and there were no general signs of increased pressure. In the hands and feet there was periosteal thickening and generalized osteoporosis of both metacarpal and metatarsal bones and their associated phalanges; there was a generalized fragmentation of the cortical layers, and several of the bones of the hands showed areas of rarefaction, a few millimetres in diameter, suggesting small cysts. X-ray examination of the sacrum revealed the presence of a spina bifida. Gottlieb and Lavine concluded that these bony lesions were neurotrophic in origin, or possibly the result of a chronic inflammatory



process. Because their patient showed cutaneous anomalies such as occur in neurofibromatosis and angiomas, Yakovlev (1935) suggested that the bony lesions were part of the general picture of congenital abnormalities in the differentiation of tissues of ectodermal derivation. He pointed out that there existed 'a form of cystic von Recklinghausen's disease of the bone which develops from the periosteal schwannomas, leading eventually to a process in the bone itself not unlike that of rarefying osteitis of Paget, with the formation of cystic cavities in the bone'.

Dalsgaard-Nielsen (1935) recorded the only other case of tuberose sclerosis in which bony lesions have been described. The changes were confined to the skull, which on X-ray examination had a 'cotton-wool' appearance due to irregular areas of hyperostosis of the cranial bones; there was also present a certain amount of intracranial calcification. Dalsgaard-Nielsen regarded these changes as representing either reactive bony processes in the nature of secondarily developed neoplasms dependent upon the underlying cerebral lesions, or as primary bony proliferations which had arisen independently of the latter, but were of a similar origin. The similarity between these cranial changes and those described by Gottlieb and Lavine is made significant by the fact that Dalsgaard-Nielsen's patient also showed evidence of neurofibromatosis, for there were pigmentary changes present on the trunk, and the fibromata of the scalp which were removed at operation had the histological appearance of neurofibromata. Dalsgaard-Nielsen commented upon this finding to the effect that his case had a special significance in that it pointed to a common link from the pathological point of view between von Recklinghausen's disease and tuberose sclerosis. In both these cases, therefore, there is evidence that tuberose sclerosis existed in association with an anomalous or incomplete form of neurofibromatosis, and the possibility arises that the bony lesions were neurofibromatous in origin.

Gould (1918) suggested that the spinal and pelvic deformities of neurofibromatosis were due to a form of bone softening which was indistinguishable from that of osteomalacia. Puech (1925) attributed the generalized skeletal involvement which sometimes occurs in neurofibromatosis to the same type of dystrophy which, occurring in the skin, forms neurofibromata. Brooks and Lehman (1924) and Lehman (1926) have shown that these bony changes are due to neurofibromatous involvement of the periosteal nerves. Such lesions excite a certain amount of bony reaction with resulting destruction and regeneration of bone. If these neurofibromatous tumours are covered by actively bone-producing periosteum, a thin shell of bone is formed over them, and they are seen on X-ray examination as subperiosteal cysts. The more these tumours involve the substance of the bone, the more extensive become the resulting bony changes. It thus follows that deformities of bone may occur with lengthening or even cessation of growth in those cases in which the epiphysis is destroyed. Winkelbauer (1927) has shown how extensive the cranial changes of hyperostosis and local atrophy may be, while Weber (1929) has incorporated the explanation of Brookes and

Lehman (1924) to account for the irregular bony thickenings of the face and skull which sometimes occur in neurofibromatosis, and which had previously been held to be due to osteitis fibrosa, one cause of 'leontiasis ossea'.

Until pathological evidence is forthcoming, all that can be said is that in the few cases of tuberose sclerosis in which bony lesions have been described, these lesions resemble in their radiological appearance the skeletal changes of neurofibromatosis, and there is an obvious similarity between these changes and the bony lesions of Case 1. It is therefore suggested that the bony changes in the frontal region of this patient are due to a hyperostosis underlying the scalp lesions and that the sclerosis and hyperostosis of the petrous bones represent their reaction to some type of localized fibromatous lesion, possibly in association with the auditory nerves deep within the substance of the petrous bones; the lesions of the hands and forearms are similarly regarded as the expression of a symmetrical involvement of the bones of the upper limbs.

The bony lesions of Case 2 are different and have never before been described in association with tuberose sclerosis. They correspond to the lesions described by Léri and Joanny (1922) in the condition which they have named melorheostosis. This condition, which is of unknown aetiology and pathology, is non-familial and affects only one limb. It is characterized by an irregular hyperostosis which runs down the shaft of the affected bone. On X-ray examination there are irregular deposits of dense bone to be seen running along the periphery of the bone shaft, the appearance resembling the drippings of a candle. Subsequent writers have suggested the name of rheostosis for the condition in view of the occasional involvement of the trunk at the site of attachment of the affected limb. There does not appear to be any other case on record in which these lesions are confined to the hand.

Rheostosis has already been described in association with craniostenosis (Muzii, 1926), trophoedema (Goldschlag, 1929) and chondrodystrophy (Hilton, 1934), all of which disorders, like tuberose sclerosis and neurofibromatosis, probably belong to that class which Weber (1939 *a*) has named 'the developmental tissue dysplasias'. Only two acquired conditions have so far been described in association with rheostosis—scleroderma (Dillehunt and Chuinard, 1936) and syphilis (Boggon, 1939). These records therefore suggest that rheostosis itself may be a type of developmental tissue dysplasia. Such a view would support the theory put forward by Zimmer (1927) that the condition is of congenital origin and is a metameric disturbance due to some embryonic defect. Weber (1939 *b*) also accepts rheostosis as a congenital developmental abnormality, and he regards it as the bony analogue of the linear dermatoses, especially the cutaneous and subcutaneous naevi in strips. The association of tuberose sclerosis and rheostosis is therefore explained on the basis that both conditions are developmental tissue dysplasias.

*Ocular lesions.* When Messinger and Clarke (1937) reported their case of tuberose sclerosis in which a retinal tumour was present, they were able to collect records of 24 other such cases from the literature, and in only five of

these cases was there a tumour of an optic disk. There can be little doubt that the retinal lesions of the two cases reported in this paper and the swelling attached to the optic disk in the case of the boy represent tumour nodules, to the occurrence of which van der Hoeve (1920, 1921, 1923, 1932) has drawn attention. According to him, nearly all the eye tumours in this condition contain cysts which have no special walls, but are merely slits in the substance of the tumour, and he has described (1921) how intra-ocular metastases may result from their rupture.

Various vascular lesions of the retina have been reported in tuberose sclerosis. Thus van der Hoeve (1920, 1921) has recorded retinal tumours in association with multiple aneurysms of a small retinal artery; Salmon (1932) described naevoid spots and naevi, while Gottlieb and Lavine (1935) noticed in their case numerous capillaries interwoven into a fine mesh, and dipping into the tumour substance which was connected by a small artery with the optic disk. The occurrence of these vascular lesions in the retina perhaps supports van der Hoeve's contention that the disorders of Bournville and von Hippel-Lindau have much in common, and belong to the same group of anomalies. According to van der Hoeve (1923, 1933), the retinal lesions of tuberose sclerosis are identical in appearance with those of neurofibromatosis, and he regards the latter as having features common to both tuberose sclerosis and the disorder of von Hippel-Lindau in that they contain neurocytes, neurofibres, and capillary angiomas. An opacity of a lens appears to be a most unusual finding in tuberose sclerosis, and only one reference to its occurrence has been found (Yakovlev and Guthrie, 1931).

*Raised intracranial pressure.* This is a rare occurrence in tuberose sclerosis, and Critchley and Earl (1932) were able to cite only very few published instances of its development. The combination of raised intracranial pressure and high protein content of the cerebrospinal fluid in the case of the boy almost certainly indicates the presence of one or more paraventricular gliomatous tumours of which numerous instances have now been recorded in this condition.

*Intracranial calcification.* The presence of numerous tiny spots of intracranial calcification indicates the occurrence of calcareous degeneration within some of the sclerotic nodules; similar calcification has been described by Marcus (1934) and Dalsgaard-Nielsen (1935). The more extensive and dense calcification, such as Macdonald (1935) described, is due to calcification of an associated gliomatous tumour.

*Subungual fibromata.* The tumours of the nail-beds of Case 1 represent subungual fibromata and resemble closely those described by Hintz (1911), Busch (1931), Elliott (1936), and James (1937).

#### Summary

1. The bony lesions which have been recorded in association with tuberose sclerosis are discussed, and the suggestion is made that such lesions are of neurofibromatous origin.



2. The bony lesions in two further cases of tuberose sclerosis are described, and comment is made on certain other rare features which these cases present.

3. It is considered that the bony lesions of Case 1 are probably of neurofibromatous origin, while those of Case 2 are identified as the lesions of rheostosis.

4. The association of tuberose sclerosis with rheostosis and neurofibromatosis is explained on the basis that all three conditions are developmental tissue dysplasias.

It is a pleasure to thank Dr. Stanley Barnes, Dr. A. P. Thomson, Dr. B. C. Tate, and Mr. Stirk Adams of the Birmingham United Hospital for their kindness in allowing me access to their patients, Dr. Harold Black for his valuable help in the interpretation of the X-rays of Case 1 and, lastly, Dr. Parkes Weber for much kindly interest and for enlightening me as to the nature of the bony lesions of Case 2.

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FIG. 1. Photograph of feet of Case 1 to show tumours of nail-beds



FIG. 2. Radiograph of skull of Case 1 (lateral view) to show appearance of frontal region and prominent markings of diploic vessels in parietal region



FIG. 3. Radiograph of skull of Case 1 (Towne position) to show sclerosis and hyperostosis of petrous bones





FIG. 4. Radiograph of forearm of Case 1 to show fibrocystic type of change in upper third of ulna



FIG. 5. Radiograph of hand of Case 1 to show areas of rarefaction suggestive of cyst formation



FIG. 6. Photograph of hands of Case 2 to show deformity of right hand



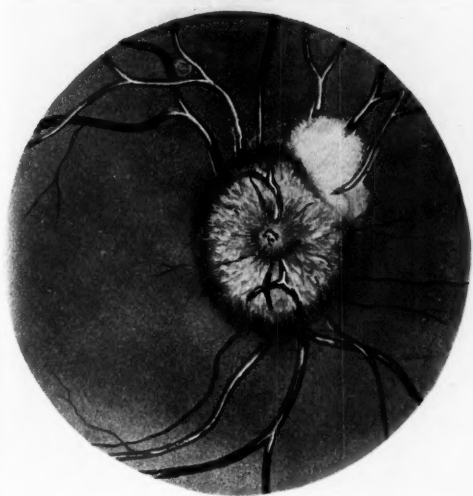


FIG. 7. Photograph of painting of right fundus of Case 2 to show tumour nodule attached to optic disk



FIG. 8. Radiograph of right hand of Case 2 to show nature of bony lesions

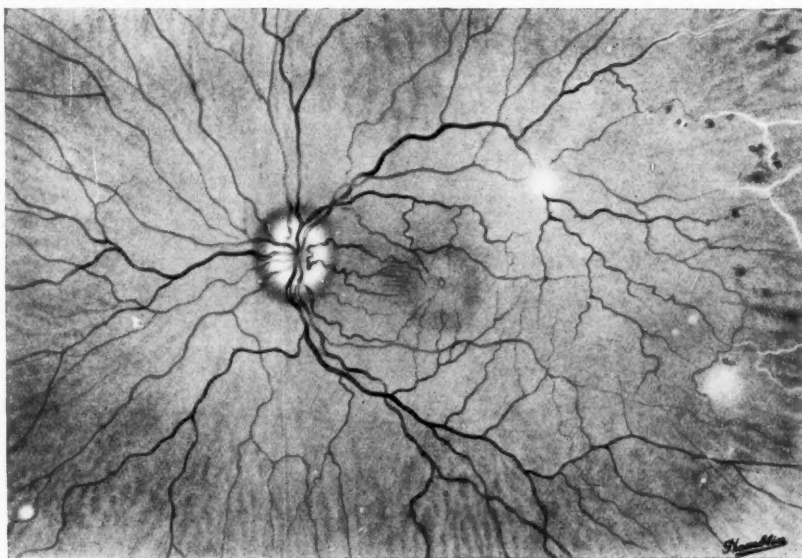
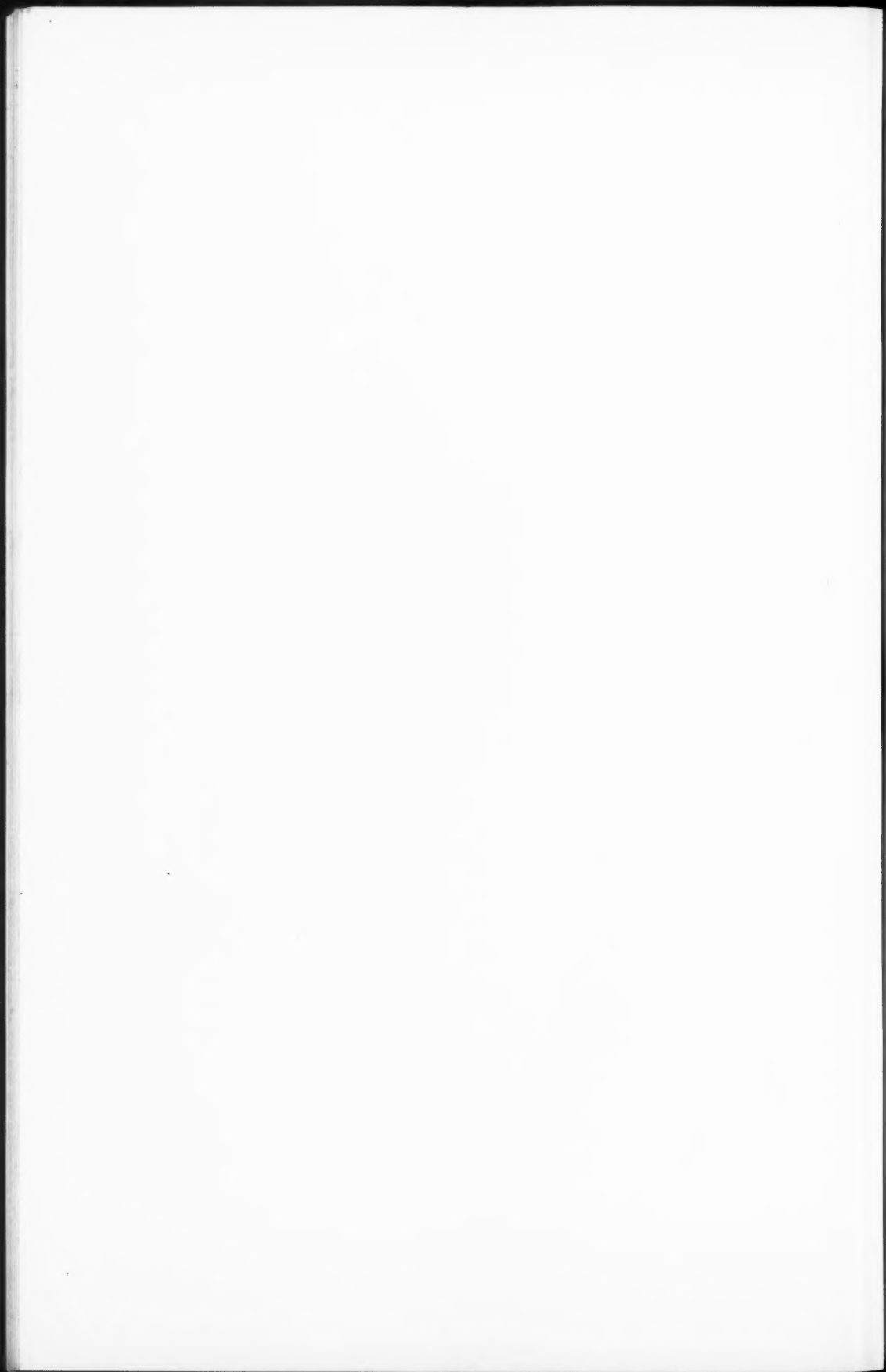


FIG. 9. Photograph of painting of left fundus of Case 2 to show tumour nodules of retina and associated vascular lesions.





## THE INTRAVENOUS DEXTROSE TOLERANCE TEST<sup>1</sup>

BY R. E. TUNBRIDGE AND E. C. ALLIBONE

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### *Introduction*

THE oral dextrose tolerance test has become an accepted procedure in the clinical investigation of unexplained glycosurias, and excellent reviews by Gray (1923), John (1922), Hale-White and Payne (1925), and MacLean and de Wesselow (1920) discuss the variations brought about by age, disease, infection, and other agencies.

Cori (1925) has shown that the rate of absorption of sugars from the intestinal tract is dependent upon the character of the sugar and not upon its concentration in the gut. This work answers in part the criticism of Beeler, Bryan, Cathcart, and Fitz (1922) who found that 22 to 68 per cent. of dextrose given by the mouth could be recovered by washing out the stomach one hour after the administration of the dextrose. The nausea sometimes experienced by subjects after the ingestion of dextrose has been shown by Hale-White and Payne (1925) to alter the result of the test considerably. The dependence of the oral dextrose test upon the degree of absorption by the alimentary canal introduces definite and uncontrollable factors in the investigation of carbohydrate tolerance. This has been well exemplified by the work of Thaysen (1929) and others in cases of idiopathic steatorrhoea, where the flat curves following the ingestion of dextrose have been proved to be due to the diminished absorption. It was largely due to the interest of one of us in idiopathic steatorrhoea and in glycosuria that we decided to investigate the possibilities of an intravenous dextrose test. Numerous investigators (see the Table) have experimented with the method, but considerable confusion has arisen from the results owing to

- (1) the varying strengths and amounts of solution used;
- (2) the varying time taken for injection;
- (3) the use of unsatisfactory controls.

In the main, two methods have been employed—the continuous administration of a weak solution of dextrose or the rapid injection of more concentrated solutions. Best (1934) considered the continuous method to be the better, but advocated the administration of fixed doses of dextrose at regular intervals as being the most likely to give the best information. Blumenthal (1903, 1905) first used the continuous intravenous method, taking as his unit of tolerance the amount of carbohydrate in grams per kilogram of body-weight which could be injected in one minute without causing glycosuria. Woodyatt,

<sup>1</sup> Received August 14, 1939.

TABLE

Author.	Date.	Number and nature of cases.	Amount of sugar in gm.	Volume in c.c.	Strength %.	Time of injection.	Glycos-uria.
Thannhauser and Pfitzer	1913	3 normals 5 liver disease 8 diabetics 4 nephritics 1 Addison's disease	35	500	7.5	15 min.	
Löwy	1916	—	40	200	20	—	
Wilder and Sansum	1917	4 normals 2 diabetics ? thyroid ? other cases	—	unlimited	20	continuous	Yes
Nonnenbruch and Szyszka	1920	13	30 to 60	2 to 300	15 to 20	30 min.	
Beumer	1921	15 hospital children	3.5 to 36.5	—	20	50 to 80 sec.	Yes
Niemeyer	1922	5 cardiac failure	10 to 40	1 to 200	10 to 20	8 min.	
Titus and Givens	1922	Normals and toxæmia of pregnancy	—	—	—	—	
Opitz	1922	6	1.78 per kilo	—	50	3 to 36 min.	
Rosenberg	1923	10 normals 10 nephritics	100	300	33	10 min.	
Jørgensen and Plum	1923	92 hospital patients	20	50	40	2 to 3 min.	Yes
Jørgensen	1926	46 hospital patients	20	50	40	2 to 4 min.	Yes
Rigler and Ulrich	1923	38 hospital patients and diabetics	1.0 per kilo 0.5 per kilo 0.33 per kilo	—	20	30 min. 15 min. 10 min.	Yes
Tisdall, Drake, and Brown (2)	1925	68 children and infants	10 c.c. per lb. of body-weight	—	10	less than 5 min.	Yes
Elias, Güdemann, and Roubitschek	1925	Two—3/12 of pregnancy	0.3 per kilo	—	30	1 to 2 min.	Yes
Davidson and Allen	1925	15 normals 12 concussion 18 head injury	25	100	25	10 min.	Yes
Lennox and Bellinger	1927	100 normals and epileptics (11 normal)	0.33 per kilo	—	20	5 min. average	Yes
Lennox	1927	? 50	0.33 per kilo	—	20	5 min. average	Yes
Rowe and Roger	1927	3 normals	0.33 per kilo	—	—	—	—
Wislicki	1928	over 10 hospital patients	8	20	40	1 min.	—
Klein and Holzer	1929	? normals, diabetics, liver disease, hypertension	3.2	8	40	20 to 25 sec.	—
Thaysen	1929	over 5 steatorrhoea	20	—	—	2 to 3 min.	—

TABLE (continued)

Author.	Date.	Number and nature of cases.	Amount of sugar in gm.	Volume in c.c.	Strength %.	Time of injection.	Glycosuria.
Schwentker and Noel	1930	? children	10 small 20 large	—	50	—	—
Törning	1931	children	10 to 20	20	54	—	—
Moncorps and Speierer	1932	60 patients (600 tests), psoriasis	8	20	40	—	—
Hartman and Foster	1932	100 overweight 100 under-weight 25 diabetics	35	—	50	5 to 6 min.	—
Rost	1932	? 1,000 (tests) dermatological	8	20	40	—	—
McKean, Myers, and Von der Heide	1935	hospital patients	0.2 per kilo	—	50	1.5 min.	—
Ross	1936	children, coeliac disease, and others	10	—	20	1 to 3 min.	Yes
Ross	1936	children	5 to 20	—	20	2 to 4 min.	Yes
Ross and Tonks	—37 1938	children	5 up to 10 kilo 10 up to 20 kilo 20 up to 30 kilo	—	20	2 to 4 min.	—
Fairley	1936 —37	over 10 normals and sprue	50	568	7	10 to 15 min.	—
Vaughan	1936 —37	few normals	50	—	—	—	—
Ghalioungui and Fikri	1937	8 anaemias	0.33 per kilo	—	—	—	—
Pijoan and Gibson	1938	4 normal adults	25	50	50	—	Yes
Crawford	1938	53 children in hospital	0.5 per kilo	—	20	20 c.c. per 45 sec.	Yes
Sheldon and Young	1938	Two— anorexia nervosa, and convalescent patient	20	—	—	—	—
Fraser, Maclay, and Mann	1938	one case of spontaneous hypoglycaemia	50	600	—	10 min.	—

Sansum, and Wilder (1915) adapted the method to the human subject, injecting the dextrose by means of a special pump. Their unit of tolerance was the amount of dextrose in grams which could be administered per kilogram of body-weight per hour without the appearance of glycosuria. In a normal human subject, the tolerance was found to be 0.8 gm. per kg. body-weight per hour. The tolerance was reduced in cases of thyrotoxicosis to 0.7 gm. per kg. per hour, and in cases of diabetes mellitus to 0.4 to 0.5 gm.

per kg. per hour. The tolerance in a variety of other conditions was studied, but not in sufficient numbers to lead the authors to draw any definite conclusions. The main criticism of the above method was the unreliability of glycosuria as a gauge for carbohydrate tolerance. Even were a catheter to be passed, glycosuria, as shown by Robinson, Derivaux, and Hewell (1935) was not necessarily an indication of the renal threshold. Further, Campbell, Osgood, and Haskins (1932) found that the renal threshold for true sugar varied from 99 to 228 mg. per cent. in different individuals. In addition, the volume of fluid to be injected and the need for a special pump rendered the method impracticable for routine clinical investigation.

The method of single injection has been widely employed (see the Table). One of the most striking features in the previous work has been the unsuitable character of the controls. Jörgensen (1926), for example, included amongst his normals a patient aged 73 years suffering from emphysema and Addison's disease, and a patient aged 77 years in whom the diagnosis was one of senility, degeneration of the spinal cord, and hypostatic pneumonia. In view of the varied technique of previous workers, we decided to investigate the response in healthy male subjects and in diseased subjects, with a standardized technique. Since this work was begun Ross (1938) and Crawford (1938) have published excellent accounts of an intravenous test in children employing a technique almost identical to that described by Allibone and Tunbridge (1939).

### *Methods*

The procedure was to inject via the median basilic vein in 3 min. 92 c.c. of a 30 per cent. solution of dextrose (Merck) dissolved in distilled water. In a few cases, the dextrose was made up in normal saline. A 50 c.c. glass record syringe with a side nozzle and special fitting was used for the injection. In practice it was found to be more convenient to handle a 50 c.c. than a 100 c.c. syringe, and little delay was caused by refilling the barrel. The selection of 92 c.c. was occasioned by the use of the 50 c.c. syringe. After allowing for the withdrawal of blood into the syringe and for the difficulty of excluding the presence of an air bubble on refilling the syringe we were unable to guarantee the accurate delivery of 100 c.c. upon every occasion. We therefore adopted the practice of reading from the 48 c.c. mark to the 2 c.c. mark. The injections were made between 9 and 11 a.m., the majority of subjects having had nothing to eat since the previous day.

Blood samples of 0.1 c.c. were taken from the lobe of the ear at intervals of  $1\frac{1}{2}$  to  $7\frac{1}{2}$  min. for at least 60 min. after the end of the injection. The ear was selected as it was easy to manipulate, a puncture of the ear was less painful than one of the finger, and it was out of the subject's sight. A special triangular puncture needle was used to ensure adequate bleeding. Upon a number of occasions, it was necessary to repeat the puncture before the end of the experiment. It was essential to keep the ear warm, and despite this,

gentle squeezing was resorted to upon frequent occasions. A careful check as to whether the degree of squeezing interfered with the blood-sugar values revealed that no appreciable error could be attributed to this fact. The time taken to collect the blood samples was 20 to 30 sec., but in a few instances the collection of the sample required 50 sec. In plotting the results the initial time of sampling has been taken as the time for the blood-sugar value. This procedure was adopted because the greater part of the sample was obtained in the first 10 sec.

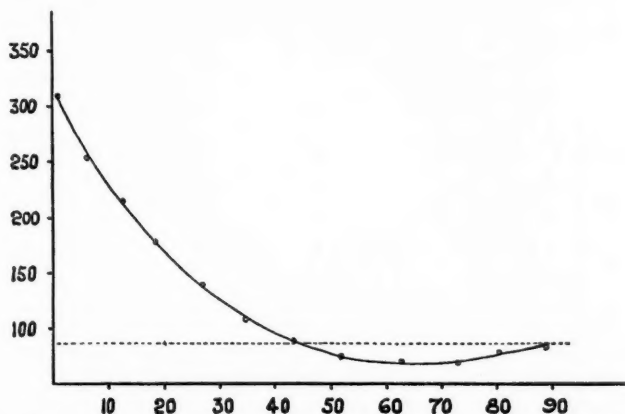


FIG. 1. Typical response in healthy adult to the intravenous injection in 3 min. of 27.6 gm. of dextrose. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

The blood was estimated by the Hagedorn-Jensen method as described by Harrison (1937). As it was not always possible to estimate the sugar immediately, sodium fluoride was added to the 0.45 per cent. zinc sulphate solution. Adopting this technique we found that it was possible to keep the blood samples in a refrigerator for three days without any appreciable change in the sugar value. A series of duplicate samples of blood have been kept as described for six days with no more change after five days than could be attributed to experimental error. With a few exceptions, all the estimations were completed within 24 hours of the blood samples being taken. The Folin and Wu (1929) method was tried, but was not found to be satisfactory for the present investigation.

### Results

Fig. 1 is a representative graph for the blood-sugar values in a healthy male adult after the intravenous injection of 92 c.c. of a 30 per cent. solution of glucose in 3 min. The general form is that of a partial hyperbola with its convexity towards the abscissae. The main features of the curve are the maximum value immediately after the end of the injection, the rapid fall

during the first 20 min., the fasting level being reached in approximately 45 min. and followed by a definite hypoglycaemic phase before the curve finally returns to the fasting level.

Fig. 2 is a composite curve showing the results of 20 tests upon 12 healthy medical students with ages ranging from 19 to 32 years. In all cases the tests were performed at or about 9 a.m., no meal having been taken for the previous 10 to 16 hours. It will be noticed that in contrast to Fig. 1 there is no hypoglycaemic phase. This is due to the hypoglycaemia of the more slowly falling

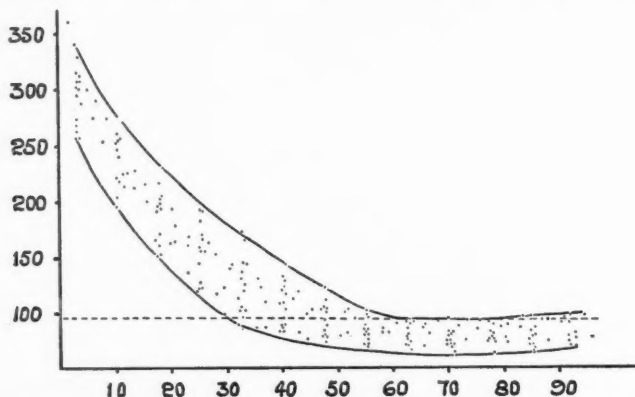


FIG. 2. Composite curve for 20 tests upon 12 healthy medical students aged 19 to 32 years and of weight 9 to 14 st. after the injection in 3 min. of 27.6 gm. of dextrose following a fast of 10 to 16 hours. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

curves being coincident with the return to the fasting level of the more rapidly falling curves. Of the 20 individual curves forming the composite curve all but three had reached their fasting level within 45 to 55 min. of the end of the injection. Of the three exceptions, one took 60 min. and the remaining two just over 30 min.

Lennox (1927) reported that the repetition of intravenous dextrose administration over a period of months led to an increasingly rapid disappearance of the dextrose. Such differences were most marked between the first and the second test, the differences between the second and third being almost within the limits of the experimental error. We have observed slight differences between the different curves for a given individual, but such differences have been slight and do not support Lennox's statement. In one subject three tests were carried out over a period of approximately one year, with little variation in the response. The subject was on a normal mixed diet and was engaged in laboratory work and in clinical practice. The test had not always been pre-arranged, as in one instance he acted as a substitute owing to the non-arrival of another subject. Similar results were obtained for two curves with other normal subjects, and such changes as occurred were very largely within the limits of experimental error (see Figs. 3, 5, and 10).



The maximum height to which the blood-sugar rises after the injection varies considerably with different subjects. We found that the blood taken one minute after the end of the injection always gave the maximum reading for the blood-sugar, and we cannot substantiate the view of Fairley (1936) and McKean, Myers, and Von der Heide (1935) that the maximum value occurs some minutes after the end of the injection. The highest value recorded in a normal subject one minute after the end of the injection was 390 mg. per 100 c.c. of blood, the lowest 312 mg. We were unable to find any correlation

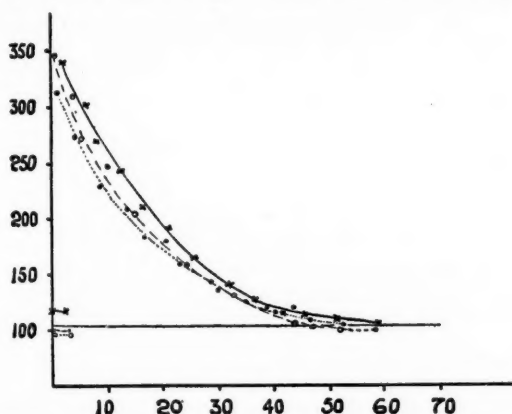


FIG. 3. The degree of variation in a normal subject. A normal man of 32 years. These tests performed during 15 months. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

between the maximum blood-sugar value and the time taken for the blood to return to normal after the injection, and we do not attach any particular significance to the former figure. Definite variations occurred in the form of the individual curves, but no significance could be attributed to these changes.

*The effect of weight.* Several workers, Rigler and Ulrich (1923), Opitz (1922), Elias, Gudemann, and Roubitschek (1925), Lennox and Bellinger (1927), Rowe and Roger (1927), McKean, Myers, and Von der Heide (1935), varied the amount of dextrose according to the weight of the subject. The weight of our normal subjects varied from 9 to 14 st., yet no variations in the maximum blood-sugar value, the form of the curve, or in the time taken to return to fasting value could be attributed to variations in weight.

*The amount of dextrose injected.* Variations in the amount of dextrose injected have a marked influence upon the results. Fig. 4 shows the response to 30 gm. and 15 gm. of glucose respectively. The same concentration of dextrose, 30 per cent., was used in each case, as we considered that the volume factor 50 c.c. compared with 100 c.c. was less likely to cause an alteration in the graph than a change of concentration from 30 to 15 per cent.

*The effect of the solvent.* Crawford (1938) suggested that the unexplained variations in the blood-sugar readings observed by Ross following the

intravenous injections of dextrose in children, were due to Ross having made up his dextrose solution with distilled water instead of with normal saline. Ross (1938) has denied this, and our results confirm the view that such variations

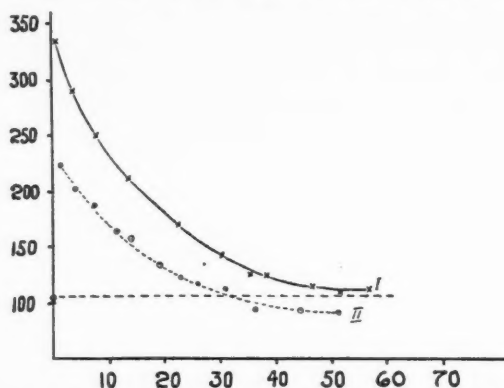


FIG. 4. The effect of the quantity of dextrose injected. A normal man of 32 years; the same subject as in Fig. 3. I. 30 gm. dextrose injected; II. 15 gm. dextrose injected. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

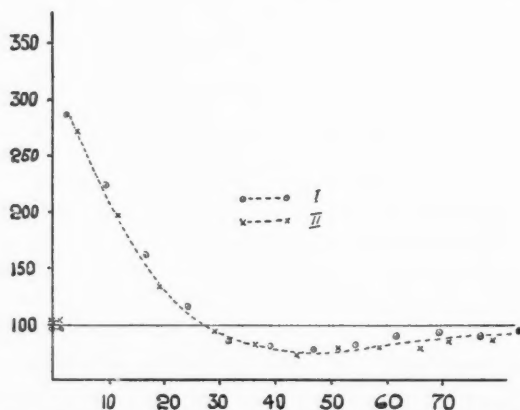


FIG. 5. The influence of solvent. A normal man of 22 years; 27.6 gm. of dextrose injected after fasting for 12 hours. I. Dextrose dissolved in distilled water; II. Dextrose dissolved in normal saline solution. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

as occur cannot be attributed to the use of distilled water. Fig. 5 illustrates the response in one individual, saline being used in one instance and distilled water in the other for the solution of the dextrose.

*The duration of the injection.* The time taken for the injection is very important. Doyon and Dupont (1901) showed that the rate of intravenous administration influenced the amount of sugar excreted. McKean, Myers, and Von der Heide (1935), using their special micro-interval method, found that increasing the time of injection from  $\frac{1}{2}$  to  $1\frac{1}{2}$  min. notably altered the



response. It is essential that the dextrose be administered as uniformly and as rapidly as possible, but small variations between 2 to 4 min. were of no significance. Ross (1938) considered that the hump effect noticed in several of his curves was more likely to occur if the injection had been prolonged. No such correlation was observed in our experiments. The consistent results obtained in healthy young male subjects led us to conclude that such results could be considered to be the normal response in the human subject. Our investigations were then extended to the variations which might occur with age and with disease.

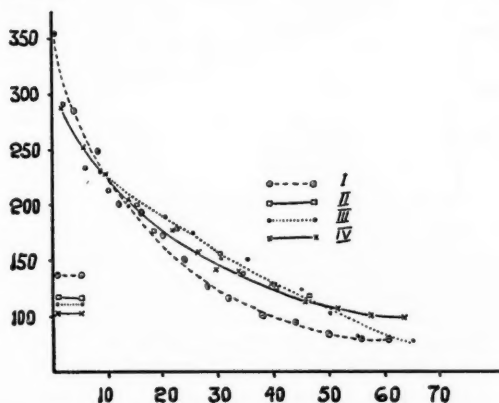


FIG. 6. Normal response in older subjects. I. A man aged 57 years, a case of cholecystitis; II. A man aged 52 years, a case of myxoedema; III. A man aged 40 years, a case of neoplasm of the chest; IV. A man aged 48 years, a case of labyrinthine vertigo; each case received 27.6 gm. dextrose intravenously. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

*The effect of age.* Fig. 6 shows responses in a man aged 40 years, a case of neoplasm of the chest; in a man aged 48 years, suffering from labyrinthine vertigo; in a man aged 52 years, suffering from myxoedema; and in a man aged 57 years, admitted for cholecystitis. These fall within our limits of normal. All our subjects over the age of 40 years were hospital patients, and whilst normal responses have been obtained, the majority of such subjects exhibited a definite delay in the return of the blood-sugar to the fasting level after the intravenous injection of dextrose. Many of these subjects had a high fasting level, a feature first described in this country by Spence (1920). Hale-White and Payne (1925) observed a similar delay in the return to fasting level with the oral glucose test. Fig. 7 illustrates a further four graphs from amongst the older group showing a delayed fall. They were from a man aged 49 years, a case of peripheral neuritis; and a man aged 65 years, a case of hemiplegia, hypertension, and obesity; the other two patients, a man aged 59 years, with Bell's palsy of five weeks' duration, and a man aged 64 years, with a Colles' fracture of two months' standing, were, apart from their physical disability, clinically healthy subjects.

*The effect of infection.* Sweeney and Lackey (1928) and Lawrence and

Buckley (1927) have demonstrated the marked effect of toxæmia upon carbohydrate tolerance after the ingestion of dextrose. The intravenous test is likewise affected by the presence of toxæmia of infection. Fig. 8 shows two

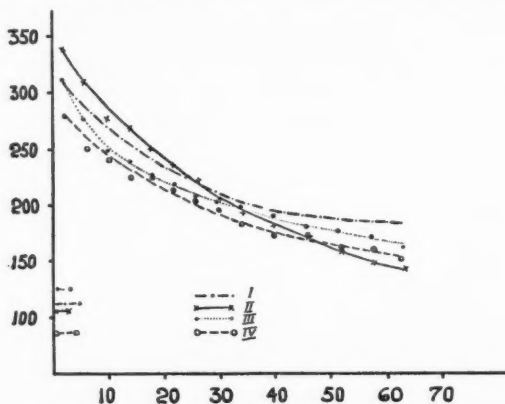


FIG. 7. The effect of age. Each case received 27.6 gm. of dextrose intravenously. I. A man aged 49 years, a case of peripheral neuritis; II. A man aged 59 years, a case of Bell's palsy; III. A man aged 65 years, a case of hemiplegia, hypertension, and obesity; IV. A man aged 64 years, a case of Colles' fracture. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

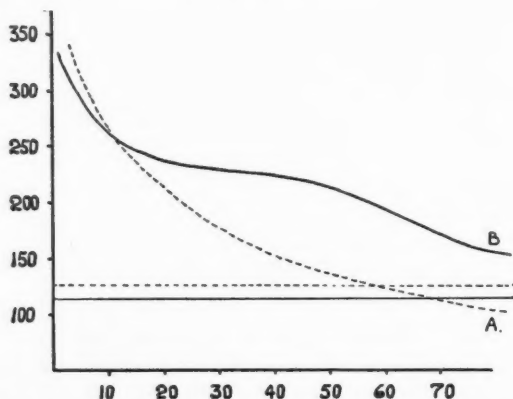


FIG. 8. The influence of infection. A man aged 23 years, a case of suppurative arthritis. Curve A—normal response; Curve B—during infection. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

curves from a male subject aged 16 years who was convalescent from a suppurative arthritis. A few hours after test 'B' had been performed, the patient developed an exacerbation of the condition. Curve 'A' shows his normal response. Another patient had a rigor following the injection and once again the result showed a diminished carbohydrate tolerance. The presence of infection has such an important bearing upon the result of the intravenous dextrose tolerance test that in our opinion no test should be undertaken if

there is the slightest suspicion that the patient has any infection. This factor probably accounts for some of the abnormal curves we have obtained in convalescent patients, and in those suffering from cholecystitis and rheumatic heart disease.

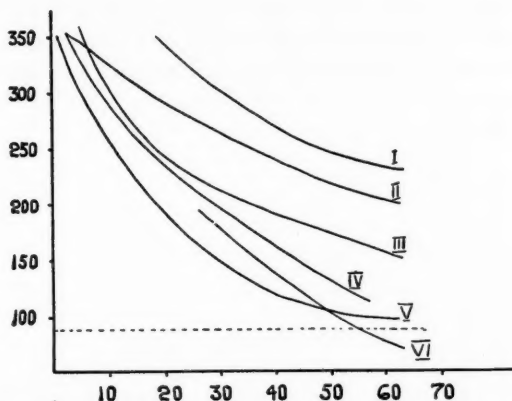


FIG. 9. Changes produced by disease. I. A woman aged 19 years, diabetes mellitus, weight 5 st. 8 lb.; II. A man aged 17 years, diabetes mellitus, weight 6 st.; III. A woman aged 17 years, Simmonds' disease, weight 6 st.; IV. A man aged 24 years, idiopathic steatorrhoea, weight 6 st.; V. A man aged 17 years, idiopathic steatorrhoea, weight 5 st. 11½ lb.; VI. A man aged 17 years, cerebral tumour, weight 6 st. Fasting blood-sugar values in mg. per cent.: I. 74; II. 90; III. 75; IV. 110; V. 100; VI. 90. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

*The effect of disease.* In studying the variations associated with disease, special attention was paid to those disorders which are primarily metabolic, such as Addison's disease, diabetes mellitus, idiopathic steatorrhoea, pituitary disorders, obesity, and thyroid disease. Studies have also been made of cases of hypertension, cerebro-vascular disease, heart failure, anaemia, leukaemia, peptic ulceration, liver disease, nephritis, and neoplastic disease. Fig. 9 illustrates the responses obtained in six young patients aged 17 to 24 years, each weighing approximately 6 st. A normal response was obtained in the patient with cerebral tumour, and the case was of interest as the boy had marked increase of intracranial pressure. The two cases of idiopathic steatorrhoea show an apparent slight degree of diminished tolerance when compared with the mean fasting level, but none when read against their own fasting levels. The remaining three cases had definite endocrine dysfunction.

*Diabetes mellitus.* All the cases of diabetes mellitus showed abnormal responses, the dextrose tolerance being diminished. It has proved difficult to correlate the response with the clinical assessment of the diabetes mellitus. This point is being investigated further and will be reported in a later communication.

*Liver disease.* In the eight cases with definite disease of the liver, the majority had a diminished dextrose tolerance, but there was nothing specific about the degree of impairment more than might be accounted for by the age of the patient or by diet.

*The effect of a light meal.* Southwood (1923) observed that an increased hyperglycaemia resulted after the ingestion of carbohydrate in a human subject who had previously been on a carbohydrate-free diet for 36 hours. Staub (1922) found that the hyperglycaemic reaction after the ingestion of 20 gm. of dextrose was less after a fast of 10 to 15 hours than after one of five hours, but that it became more marked after a fast of 24 hours. The normal hospital patient has tea at about 3.30 p.m., a drink with possibly

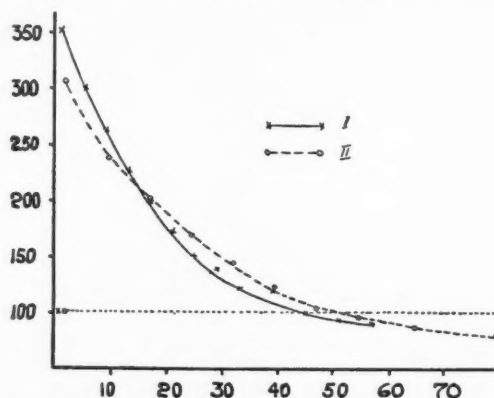


FIG. 10. The effect of a light meal. A normal medical student aged 21 years. I.  $2\frac{1}{2}$  hours after a light meal; II. Fasting. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

bread and butter at 6 p.m., and nothing further until breakfast next morning at 6 o'clock. When he has been starved for the test it is possible for him to have had nothing to eat for 18 hours, although the usual time is only 15 hours. In a normal subject, after a meal the blood-sugar has returned to fasting level within  $2\frac{1}{2}$  hours. Further, any insulin secreted will have exerted its maximum effect within four to six hours. It was therefore decided to compare the results of the intravenous injection of dextrose after a light meal with those from the same subjects after fasting for 10 to 16 hours. It was not considered advisable to perform a series of tests, two, four, and six hours after a meal in a single individual, but in a series of normal medical students and in hospital patients a test has been made at varying intervals after a light meal. Fig. 10 shows the respective graphs for a healthy medical student, I =  $2\frac{1}{2}$  hours after the meal, II = fasting. Parallel results were obtained in a series of 12 healthy medical students. Our experience has shown that a light breakfast, such as fruit, tea, toast, and marmalade, taken four to five hours prior to the test, does not alter the main results.

*The effect of diet.* The most extensive studies on the effect of diet on the carbohydrate tolerance in the human subject have been made by Himsworth (1934) and Sweeney (1927). It seemed advisable in view of these findings to determine the order of the changes, if any, caused by diet upon the intravenous dextrose test. The subjects chosen were all hospital patients. Three

of the subjects were confined to bed throughout the whole of the experiments, two were ambulatory patients, and one was an out-patient. The ages ranged from 16 to 68 years. The diet was carefully supervised, all food being weighed, and the patients were so co-operative that we were confident that the diet had been strictly adhered to in every case. Our procedure was to perform an intravenous dextrose test on the fasting subject, followed the next morning by an insulin depression test, the dose of insulin being 10 units. The subject was then placed on a low carbohydrate and high fat

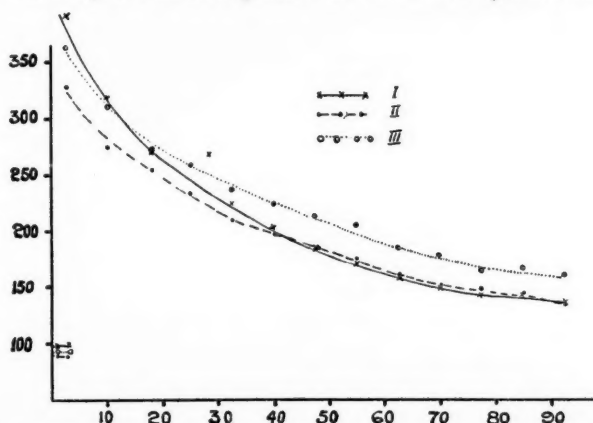


FIG. 11. The effect of diet. A man aged 68 years, a case of fractured femur. I. After 14 days on high carbohydrate and low fat diet, C. 455 gm., P. 77.5 gm., F. 30 gm.; II. After 14 days on ordinary hospital diet; III. After 14 days on low carbohydrate and high fat diet, C. 50 gm., P. 77.5 gm., F. 210 gm. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

diet, 50 gm. carbohydrate, 77.5 gm. protein, 210 gm. fat for 14 days. On the thirteenth or fourteenth day the intravenous test was repeated, and was followed the next morning by an insulin depression test. The subject was then transferred to a high carbohydrate and low fat diet, 455 gm. carbohydrate, 77.5 gm. protein, 30 gm. fat, for fourteen days, and the intravenous dextrose test and the insulin depression test were repeated. The insulin depression test was always done on the day following the dextrose test. The heat value of both diets was approximately 2,400 calories. Himsworth (1935) did not consider the absolute calorie value to be of any significance in animal work, and that only the carbohydrate content was of importance. Fourteen days is a longer time than most workers allow for stabilization on a diet of fixed carbohydrate content, but in view of the experience of one of us with other metabolic investigations and the careful work of Scott and Dotti (1932) upon rabbits, we consider that deductions based upon a shorter period are open to criticism. Fig. 11 represents a typical result of such an experiment. It will be seen that the original curve and that produced after the period on the high carbohydrate diet were almost identical, whilst the curve produced after the period on the low carbohydrate diet revealed a definite impairment of dextrose tolerance.

The effect of diet has been observed indirectly in several of our other experiments. A man, aged 51 years, suffering from jaundice following the administration of arsenic, gave a normal response. The other cases of jaundice in the series all exhibited a diminished tolerance. The case referred to, however, had been on a liberal carbohydrate diet for rather more than a week, with calcium and 20 gm. dextrose four-hourly. In view of the later experimental evidence we consider that these facts most probably accounted for the result obtained.

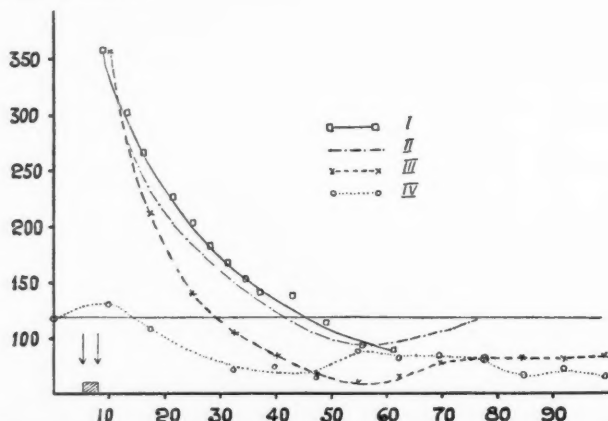


FIG. 12. The effect of administering 10 units of insulin intravenously, with dextrose. A man aged 20 years, weight 9 st. I. Normal curve; II. Hypothetical curve (curve III corrected for insulin depressant action); III. Curve after 10 units of insulin administered intravenously with dextrose; IV. Insulin depression curve after 10 units of insulin administered alone. The arrows indicate the beginning and end of the injection of the dextrose. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

*The effect of insulin.* The precise role of insulin in carbohydrate metabolism is still undecided, but in view of its undoubted importance we deemed it advisable to determine what effect, if any, insulin administered either intravenously or subcutaneously, had upon the intravenous dextrose tolerance test. The dose selected was 10 units, and the same phial was used as the supply for all the experiments upon normal subjects. Three normal subjects had tests when 10 units of insulin were administered intravenously with the dextrose, and in three others insulin was given subcutaneously 20 to 25 minutes before the dextrose. In all the subjects the effect of the same dose of insulin administered alone and by the same route was observed after an interval of a few days. Fig. 12 illustrates the results obtained after the administration of intravenous insulin with and without dextrose, and Fig. 13 shows similarly the results with the use of subcutaneous insulin. In all cases the effect of insulin was to deflect the curve to the left, that is, to increase the carbohydrate tolerance. There was, however, no distortion of the shape of the graph, all the blood-sugar values falling upon the curve. The smoothness of the curve following insulin administration was striking. In a similar



series of six tests performed with dextrose solution alone, we obtained one or two points which lay off the curve at a greater distance than could be accounted for by experimental error. No such points were obtained when insulin had been administered, and there was never any suggestion of humping. These results confirm the experience of Noltie (1938) with rabbits. Himsworth (1935) has stressed the importance of selecting for comparison dextrose curves which start at the same fasting level. In the human subject one is dealing with so many uncontrollable variables—amongst which must

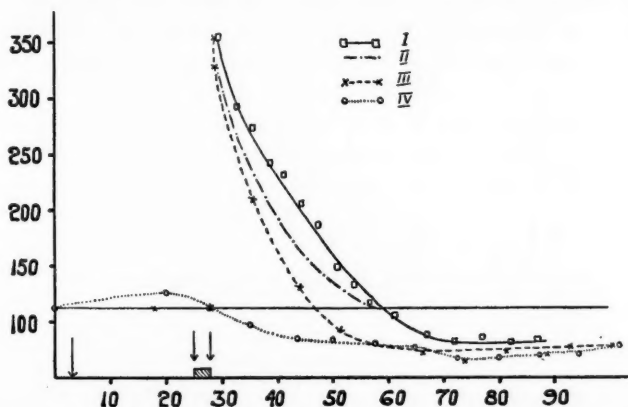


FIG. 13. The effect of subcutaneous insulin. A man aged 22 years, weight 13 st. I. Normal curve; II. Hypothetical curve (curve III corrected for insulin depressant action); III. Curve after 10 units of insulin administered subcutaneously followed 20 min. later by injection of 27.6 gm. of dextrose; IV. Insulin depression curve after 10 units of insulin only, administered subcutaneously. Single arrow indicates the injection of insulin; double arrow indicates the injection of dextrose. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

be included emotional factors (Cannon, Shohl, and Wright, 1911; Griffith, 1923)—that it is extremely difficult to fulfil the above condition. In the insulin experiments the fasting level of the two subjects, whose curves are reproduced, was high, a feature we have noticed in other fasting subjects. Both had travelled to the laboratory before the tests were performed, a fact which may have influenced the high fasting level (Hale-White and Payne, 1926). In the insulin experiments it was observed that if allowance was made for the depressant effect of insulin upon the blood-sugar, the fasting level being the same, the time taken for the blood-sugar to reach fasting level after the administration of dextrose with insulin was very little different from the time taken following the administration of dextrose alone. We do not attach any particular significance to these results, as they may be due to the arbitrary selection of the doses employed.

*Anomalous curves.* Opitz (1922), Jörgensen and Plum (1923), and Ross (1938), have observed certain unexplained irregularities in the blood-sugar values following the intravenous administration of dextrose. Occasional anomalous isolated readings have been obtained in the present work, and



have been attributed to a defect in the technique. Quite distinct from the latter, however, 15 of the tests showed irregularities of a definite character, Fig. 14.

*Straight line.* In three instances—a youth, aged 17 years, with toxic jaundice; a man, aged 64 years, with diabetes mellitus and obesity; and a woman, aged 28 years, with splenic anaemia—the graph of the blood-sugar values plotted against the time after injection was a straight line.

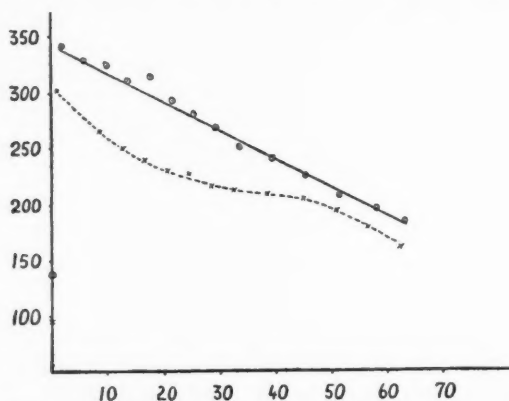


FIG. 14. Anomalous curves illustrating a typical straight and a typical humped curve. Ordinates = blood-sugar in mg. per cent.; Abscissae = time in minutes.

*Hump.* In 12 cases there has been a definite tendency to a humping of the curves, a feature commented upon by the workers named above. Fig. 8 illustrates our most marked example of humping. In two of these cases the tests have been repeated. In one—a man, aged 34 years, suffering from atheromatous gangrene of both legs (later proved by post-mortem examination)—the abnormality persisted. In the other—a man, aged 48 years, with a cerebral tumour—the second test yielded a smooth curve. In some instances the degree of humping was very slight, and had it been observed only once or twice we might have attributed it to experimental error. The time of occurrence, either 20 to 40 or 40 to 60 min. after the end of the injection, is a feature of considerable interest, and one we consider to be more than a coincidence. The diagnoses in the cases showing a humped curve were as follows:

- Woman, aged 44 years, obesity.
- Woman, aged 43 years, splenic anaemia.
- Man, aged 34 years, thrombosis of the common iliac arteries.
- Man, aged 56 years, fractured tibia and fibula.
- Woman, aged 41 years, diabetes mellitus.
- Woman, aged 39 years, cerebral tumour.
- Woman, aged 48 years, rheumatic heart disease.
- Man, aged 63 years, hemiplegia.
- Man, aged 51 years, myeloid leukaemia.
- Man, aged 53 years, diabetes mellitus.

Man, aged 65 years, diabetes mellitus.

Man, aged 23 years, healthy medical student.

The most striking feature about these results was that out of 42 tests performed upon medical students only one gave a slight degree of humping, whereas amongst 92 tests upon patients, 14 humped curves or straight lines were obtained. In the case of the student and in one of the patients definite pain was experienced during the injection, but in the other instances it was difficult to find any common factors. Our evidence does not substantiate the view of Ross (1938), that humping is more likely to occur if the time of the injection is prolonged. Noltie (1938) in a personal communication to one of the authors, stated that he had observed similar effects following the intravenous administration of dextrose in rabbits, and that the administration of a small dose of insulin abolished these effects. Best (1934) has stressed the importance of the adrenal glands in the control of carbohydrate metabolism, and we consider this to be a possible explanation of the phenomenon, although it is one which it is difficult to prove.

*Glycosuria.* Glycosuria has been reported by several workers after the administration of intravenous glucose by means of a single injection. Beumer (1921) 0.8 to 1.3 gm., Rigler and Ulrich (1923), Davidson and Allen (1925) 0 to 2.8 gm., Elias (1925), Tisdall, Drake, and Brown (1925), Jörgensen and Plum (1926), Lennox and Bellinger (1927) 1.0 to 2.0 gm., Ross (1936), and Pijoan and Gibson (1938) 1.8 gm.

Jörgensen and Plum (1926) did not find glycosuria after the administration of 16 gm. of dextrose intravenously, but it always occurred after the injection of 19 to 21 gm.

A systematic study of the urinary extraction of dextrose after the test has not been made in all experiments. In the majority of students, and in some patients, however, a systematic estimation has been made. The procedure has been for the subject to pass a sample of urine some 20 to 30 minutes after the end of the injection and again after the last blood sample has been taken. In some cases it was possible to obtain only the latter specimen. The precaution was taken to ensure that the patient was not normally subject to glycosuria, and in the case of the diabetics the bladder was emptied just before the injection was given. In criticism it may be suggested that a further sample of urine should have been collected after the taking of a glassful of water after the last blood sample. This was done on two occasions, but no reduction was obtained with the Benedict qualitative test on the urine passed. Hospital patients in whom a catheter was *in situ* proved unsatisfactory controls for the test, as, quite apart from age, all of them had an associated infection.

In normal medical students the amount excreted varied from 1.4 to 2.3 gm., the mean being rather less than 2 gm. There was no correlation between the amount of dextrose excreted and the time taken for injection, or between those cases in which the dextrose was administered dissolved in saline or in distilled water, whether the test was performed after fasting or

after a light meal, or upon the order in which repeated tests were done upon one subject. It was observed in one case that no further dextrose was passed after 20 min., and in the cases where two samples were obtained the first one contained the major portion of dextrose. The results with patients are striking in so far as several of the cases of diabetes showed no greater excretion than was obtained with normal subjects. It must be stated, however, that these cases were fully stabilized.

*Complications.* Complications following the intravenous administration of dextrose in the human subject have been reported by Thannhauser (1913), Bernstein and Falta (1918), Schenk (1920), Opitz (1922), Lennox and Bellinger (1927), and Jörgensen and Plum (1926). The chief complications reported here have been pyrexia, rigors, general malaise, and headaches. Jörgensen (1927) noted pyrexia in four of his first 75 cases, but after the use of freshly distilled water for the solution of the dextrose he had no complications in a further 50 cases.

We have had 15 complications in 132 tests. The reactions with four exceptions have occurred in medical students, and of these four exceptions three were in persons following their normal occupation, and attending the hospital as out-patients. The remaining subject complained of headache and shivering, and shortly after the injection developed an exacerbation of a chronic suppurative condition of the knee-joint. He had had previous similar attacks, and it was difficult to assess what part, if any, was played by the injection in causing the rigor. In all, three subjects had complications with two tests each, but the remainder of the subjects had no complications when further tests were carried out upon them. In one subject who had three tests, the complication was observed after the second test only.

The complications have comprised pain in the arm and pyrexia, two cases; pain in the arm, eight cases; headache, three cases; rigors, two cases. The two cases of pain in the arm associated with pyrexia afforded the most serious complications. One was possibly due to the dextrose solution. In each instance the subject developed a definite phlebitis of the left arm, extending from the antecubital fossa to the axilla, within twelve hours of the injection; the left arm was used for the injection in all right-handed subjects. The phlebitis was accompanied by general symptoms such as malaise, headache, nausea, and by pyrexia. The pyrexia in both instances lasted for two days, and the whole condition had subsided within one week of the injection. There were no sequelae. The history of the remaining cases who complained of pain in the arm, but who experienced no pyrexia and no general symptoms, was striking. In no case did the subject experience pain until at least three days after the injection. Further, all had in the meantime participated in vigorous exercise or work. The following history is typical. A male medical student, aged 23 years, injection given on Saturday at 10 a.m. No difficulty experienced with the injection, time taken 3 min. No complaint during or immediately after the injection. Participated in vigorous exercise during the week-end. First complained of

tenderness of the left arm on the following Wednesday. On examination the median basilic vein was palpable for a matter of 2 to 3 in., the most distal point being one inch above the site of injection. There was slight tenderness, no severe pain, and no general symptoms. The condition subsided in three days.

In two cases only had any difficulty been experienced with the injection, so that this factor cannot be blamed. We have, on the contrary, been surprised at the lack of complications in the few cases where technical difficulties accompanied the injections. If a little of the dextrose is injected into the subcutaneous tissues there follows immediately a severe pain lasting a few minutes, passing off gradually without any after effects. Further, there was no question of the dextrose solution being at fault, apart from the one exception named, as in some instances the solution was used for two subjects, one only having subsequent complications.

Two subjects complained of headache, one of them having it after each test. The headache began two to three hours after the injection, and lasted for several hours. In neither instance was the subject normally liable to headache. In view of the effect of hypertonic dextrose solution in reducing intracranial pressure, we were surprised that this complication did not occur more frequently.

It is doubtful whether the injection can be held responsible for the rigor in one of the two subjects who experienced this complication, as he was convalescent from a suppurative arthritis of the knee and had had, it was later discovered, several similar attacks.

It might be argued that all the complications were not observed, and therefore that their importance has been under-estimated. The first complication followed the second test, the first test having been performed on one of the authors. Therefore we informed all subjects that they might experience pain or other symptoms, and asked them to report any such manifestation at once. No case of ulnar or peripheral neuritis has been observed to follow the test. The outstanding feature has been the absence of any complication after the injection of dextrose in patients who were confined to bed.

#### *Discussion.*

The method described for an intravenous dextrose tolerance test has yielded consistent results with healthy young men. We attribute this to the careful selection of our material and to the criteria adopted in the interpretation of the findings.

In the case of the oral dextrose tolerance test it is the practice of Continental and American workers to vary the dose of dextrose with the weight of the subject, whereas in Great Britain it is customary to employ a standard dose of 50 gm. for adults. Many previous workers (see the Table) using the intravenous test, have varied the amount of dextrose injected with the weight of the subject. This procedure we consider unjustified for the normal

variations in weight, and we agree with Törning (1932) when he stated that 'a fat person is a thin one with a sack on his back'. It has been the practice in the present work to use a standard dose of 27.6 gm. of dextrose. The weight of the normal subjects varied from 121 to 198 pounds, and no specific effect could be assigned to variations of weight within these limits.

The sex factor in the young adult group has not been studied. In the hospital subjects observed no specific fact could be attributed to this factor in any age group. Further work upon healthy young female subjects is desirable in order to exclude the possible influence of endocrine factors associated with the menses upon the rate and mode of disappearance of intravenously administered dextrose.

The importance of the diet immediately prior to the making of the test has been shown, and the lack of control of this factor may account for some of the variations in the recorded results of other workers.

Some of the difficulties in the interpretation of previous results arise from the employment of different criteria. In the case of the fasting blood-sugar level a theoretical mean value might be taken as the basic level or the value in the subject immediately prior to the test. The latter value has been used in the present work, although it has not always been possible to obtain identical fasting levels for consecutive experiments on every subject. The maximum blood-sugar value after the injection has been used by Ross (1938) and Jørgensen (1926-27) for comparing their results. We found great variation in the maximum blood-sugar reading after the injection in different individuals, and even in the same individual. No common factor, such as the time taken for the injection, any excessive local trauma, the previous fasting blood-sugar level, whether the dextrose was dissolved in saline or distilled water, or even the taking of a light meal three hours before the test, could be held responsible for the variations encountered. Similarly, concerning the shape of the curve, no factor or factors were observed which we could prove to be responsible for the form of a given curve. The repetition of the test under identical experimental conditions revealed considerable differences in the maximum height of the curve, but only slight differences in the detailed form of the curve, and little variation in the time taken to reach the pre-injection fasting blood-sugar value. We therefore consider the latter to be the only significant reading in the test described.

The methods described by Jørgensen (1926) and Ross (1938) in measuring the area of the graph, based as they are upon the maximum blood-sugar value and the general form of the curve, we do not consider to have any real scientific or even comparative significance.

Sixteen tests were performed on ten healthy medical students and in all circumstances the blood-sugar value had returned to the pre-injection level within 45 to 55 min. This degree of variation in the selected cases is appreciable, but when repeated tests for a given individual are compared the most striking feature is the constancy of the time taken to return to fasting level.



The degree of group variation with the oral dextrose test is in our experience greater than that encountered in the intravenous test, so that we do not feel that the argument of individual variation with the intravenous test is sufficient to discountenance the value of the test.

The reason for the more rapid return to pre-injection level in certain individuals as compared with others is not readily explicable, and work on this point is in progress. We would say, however, as a result of our present experience, that in a normal healthy young adult, after injection intravenously of 27.6 gm. of dextrose, the blood-sugar value should have reached the pre-injection level within 60 min.

What is the immediate fate of the injected dextrose? Is it excreted, stored, or metabolized? The complete answer to this question is difficult because there is the possibility of the removal taking place in two stages, an immediate one and a late one. The blood findings suggest strongly that this is the case. The highest blood-sugar value recorded 45 sec. after the end of an injection was 394 mg. The duration of the injection in this case was 2 min. 30 sec. Assuming the blood-volume of the normal subject to be 5 litres, a figure considerably higher than that quoted by Gibson and Evans (1937), the blood-sugar value immediately after the injection of 25 gm. of glucose should be approximately 600 mg. That is, within approximately 2 min. of the mean injection time 10 gm. or 40 per cent. of the injected dextrose has been removed from the blood-stream. It is difficult to conceive that this amount of dextrose has been completely metabolized within this short interval. Urine excretion does not appear to be an important factor in the removal of the injected dextrose. In the tests described the glycosuria never exceeded 2.5 gm. in healthy men, which is approximately 10 per cent of the injected dextrose. This figure compares with that of Davidson and Allen (1925) of 0 to 2.8 gm. after 25 gm. injected, and of Pijoan and Gibson (1938) of 1.8 gm. after 25 gm. Further, there is the experimental work of Kleiner (1916) who found that, even in nephrectomized animals, after the injection of 27 gm. of dextrose he was unable to account for 26.56 gm. of the injected material. It would thus appear that the loss of dextrose by the kidneys cannot account for the rapid disappearance of dextrose from the blood-stream. Further, of the 2.5 gm. excreted in our experiments, some portion of this at least is excreted after the first two minutes, so that we cannot deduct the total amount excreted in the urine from the 10 gm. which disappears from the blood-stream within the first two minutes.

It has been suggested that changes in the blood-volume might account for some of this apparent loss from the blood-stream. We have no precise data on this point. Jørgensen (1923) and McKean, Myers, and Von der Heide (1935) determined the changes in blood-volume by measuring the changes in the haemoglobin content of the blood. We did not consider this method sufficiently accurate, and hesitated in the early stages to make repeated hematocrit readings as we felt that repeated venepuncture might have a disturbing influence on the blood-sugar values. Pijoan and Gibson (1938) using

the Evans blue method (Gibson and Evans, 1937) for measuring the blood-volume, found that after the injection of 25 gm. of dextrose dissolved in 55 c.c. of water, there was little change in the blood-volume. There was a slight immediate increase of 4 per cent, followed by a diminution of 5 to 6 per cent after 20 to 30 minutes. Further, they found that 87.5 per cent of the injected dextrose had disappeared from the blood-stream within four minutes. Changes in blood-volume therefore do not appear to afford an adequate explanation of the rapid disappearance of dextrose from the blood-stream. Whether the injected dextrose is stored or metabolized, and what is the site of these activities, has not been fully studied in the present work. Sufficient data are not available concerning changes in the blood-volume, blood lactic acid, inorganic phosphate, and chloride content of the blood, nor of the changes in the respiratory quotient, to enable us to discuss in further detail at this stage the many metabolic problems concerned in the disposal of the injected dextrose, and in consequence we shall not enter upon a discussion of the bearing of previous work upon the probable fate of the injected dextrose. This aspect of the problem will be dealt with in more detail in a subsequent publication.

In the present study, however, cases exhibiting gross hepatic damage and gross endocrine dysfunction were purposely selected with a view to determining whether such conditions were associated with any specific change in the response to the intravenous administration of dextrose. Certain cases of liver disease or damage did reveal an impaired tolerance, but these changes were not greater than those observed in other conditions which clinically had no evidence of hepatic damage. The assessing of hepatic damage is extremely difficult, either clinically or by means of laboratory tests, so that the lack of correlation between the response to intravenous dextrose and between the clinical and laboratory data cannot be considered adequate justification for stating that the liver does not play an important part in the regulation. The two laboratory tests used to assess liver damage were the hippuric acid test and the laevulose tolerance test (Herbert, 1938).

#### *Summary*

1. A standard intravenous dextrose tolerance test is described in which 27.6 gm. of dextrose are injected intravenously in three minutes.
2. One hundred and thirty-two tests have been performed, 40 upon healthy medical students and 92 upon hospital patients.
3. In the test described the blood-sugar reading is shown to return to the pre-injection level within 60 min. in healthy young men.
4. Repetition of the test upon the same healthy young man revealed a remarkable degree of constancy in the time taken for the blood-sugar to regain the pre-injection level, but the actual time varied for different individuals.
5. The evidence submitted shows that the response is altered by age, by infection, by disease, by diet, by the amount of dextrose injected, and by



insulin, but not by the normal variations in weight or by the substitution of normal saline as a solvent for the dextrose instead of distilled water.

6. It has not been possible to ascribe any specific variation to a particular disease.

7. Certain abnormal curves were obtained and their possible significance is discussed.

8. Glycosuria has been observed in all the urines examined, varying in amount from 0.25 to 2.4 gm. in healthy young men.

9. Complications directly attributable to the injection of the dextrose solution have been encountered in 15 cases. Details of the complications are described.

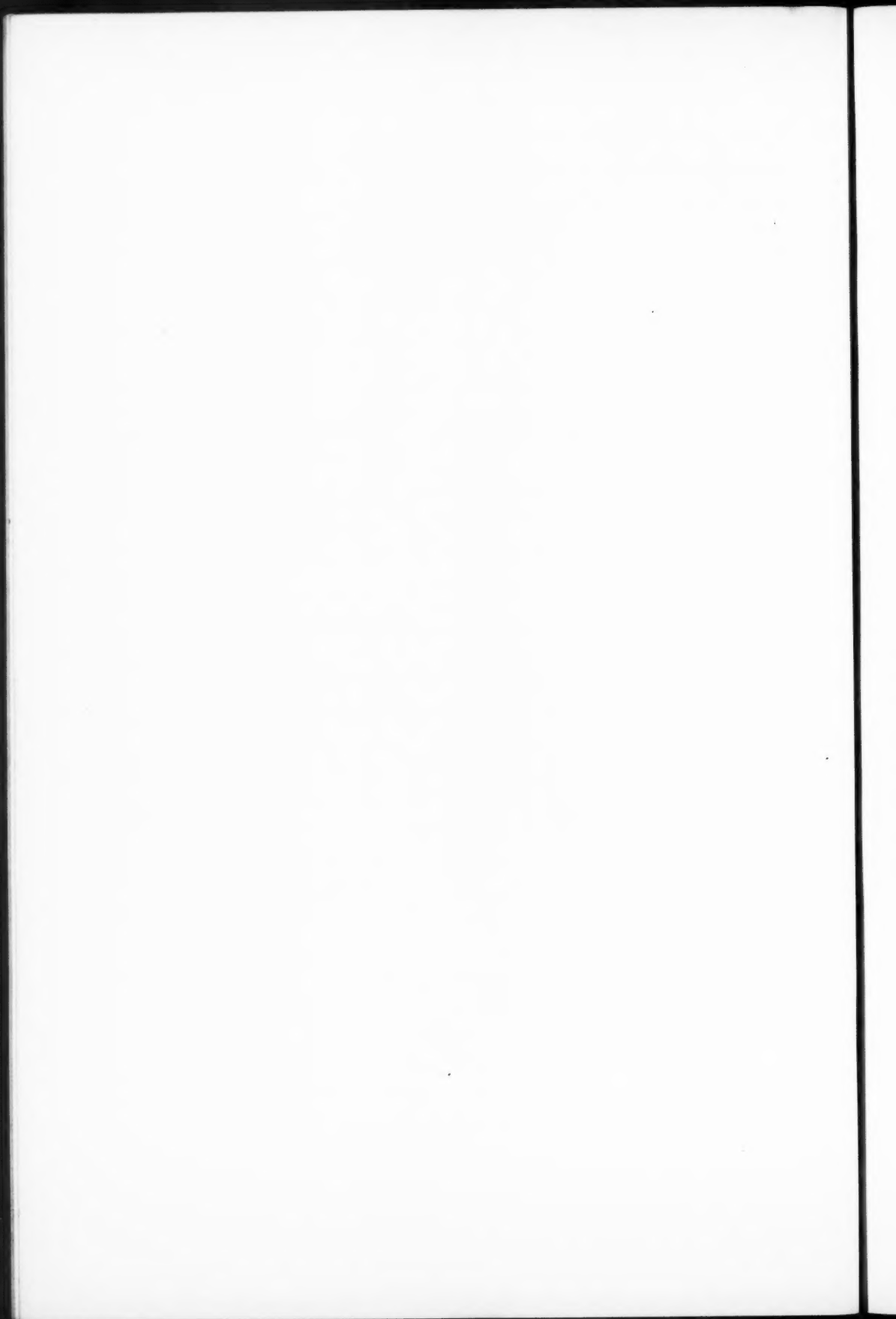
We should like to express our thanks to the medical students who so readily volunteered to help with this study, to Mr. J. Blackburn for technical assistance, and to the members of the Honorary Staff of the General Infirmary, Leeds, for allowing us to have access to the clinical cases under their care.

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## ACUTE NEPHRITIS IN CHILDHOOD, WITH SPECIAL REFERENCE TO THE DIAGNOSIS OF FOCAL NEPHRITIS<sup>1</sup>

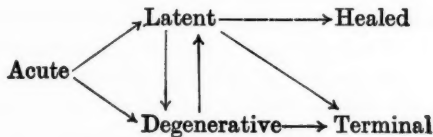
BY W. W. PAYNE, AND R. S. ILLINGWORTH

(From the Hospital for Sick Children, London)

ANY one who has studied the numerous papers dealing with the terminology and prognosis of acute nephritis in childhood must have been left with a feeling of complete bewilderment. In many cases the dominance of one or other feature has been used as the basis of an intricate clinical classification. Although such classifications may be of some value at the bedside, they ultimately confuse the issue because they cannot be correlated with the underlying pathology. The dominance, furthermore, of one or other of these features plays only a transient part in the natural history of the disease, and has no bearing on the eventual outcome.

The present paper is an attempt to study from the purely clinical aspect the validity of certain of these clinical classifications. It began with the observation by one of us (W. W. P.) several years ago, that considerable nitrogen retention frequently occurred in the so-called 'focal' nephritis, whereas practically all writers deny that such nitrogen retention does occur. Consequently a large number of blood-urea estimations have been performed in this hospital on cases of diffuse and focal nephritis, in order to determine whether there was any greater tendency to nitrogen retention in one type than in another. Further study of these cases led us to question the usefulness of the current distinction between focal and diffuse nephritis. The purpose of the present paper is to determine whether this distinction is justified by the clinical features and eventual outcome of the two conditions. In studying these cases of focal nephritis certain difficulties appeared. It was found that the accepted diagnostic criteria did not fit the cases we were seeing, and it became necessary to study the whole range of acute nephritis of childhood. We have therefore reviewed 301 cases of acute nephritis seen in this hospital, and mentioned some 64 further cases which have been seen in stages other than the acute.

*Classification.* Addis (1925) has presented a classification of nephritis, as follows:



<sup>1</sup> Received August 22, 1939.

The distinguishing features of the acute, latent, and degenerative stages are summarized in Table I. The terminal stage is that commonly referred to as chronic interstitial nephritis, and it must be understood that the condition may last for several years. The scheme shows how acute nephritis may pass on to the latent stage or to the degenerative stage. The former is by far the

TABLE I

*Clinical Features of the Acute, Latent, and Degenerative Stages of Nephritis.*

Features.	Acute.	Latent.	Degenerative.
Condition of patient	Nothing characteristic. Well or ill	Very well and symptomless	Gross oedema usually present
History of preceding acute infection	Usually present	—	May be history of a preceding cold. Very rarely history of preceding acute infection such as acute tonsillitis or otitis
Oedema	None or moderate	None	Usually very gross
Albuminuria	Moderate	Usually very slight	Massive
Blood	Nearly always macroscopic. Always large numbers of red blood-cells on microscopy	None, or a few red blood-cells on microscopy	Very few red blood-cells on microscopy; may be none for periods of several weeks
Casts (granular) (cellular)	Nearly always present, often in large numbers	Usually absent or very few.	Often absent or very few
Blood-urea	Usually raised in first few days, usually rapidly falling to normal	Normal	Normal or raised. If raised it usually remains high for a long time with remissions and exacerbations
Blood-pressure	May be raised in first few days, usually rapidly falling to normal	Normal or rising	Normal or raised. If raised it usually remains high for a considerable length of time
Oliguria	Fairly frequent	None	May be present
Course	Usually resolves rapidly. Outcome as in diagram.	Continues, with eventual outcome as shown in diagram. May last for years	Very chronic. Usually passes on into irreversible terminal stage (chronic nephritis), May pass into latent stage

commoner course of events. The latent stage may pass on to the healed, terminal, or degenerative stages; the degenerative very rarely to the latent stage, but almost invariably to the terminal stage. It is essential to distinguish the acute stage of the disease from the degenerative. Failure to do so has been responsible for most of the confusion which exists about the terminology of nephritis. The difficulty in recognizing the degenerative stage is chiefly due to the fact that many cases are seen in this stage with no history of a preceding acute attack. Often the patient is able to say that a cold or chill preceded the onset of oedema by a day or two—not a surprising occurrence in view of the prevalence of the common cold—and this is then regarded as the cause of the condition. That the condition which we call the degenerative stage of nephritis is in fact merely a late phase of the disease is shown

by Addis (1925, 1931), Snoke (1937), and others, who by means of the sediment count followed cases from the acute stage of nephritis, through the latent stage to the degenerative stage, and thence through the terminal stage to death and autopsy. Details of the sediment count are given by Snoke (1937).

Of the 42 cases seen by us in the degenerative stage, 14 had a known preceding acute nephritis one to seven years earlier. The clinical and biochemical picture of those who had had a previous known acute attack was identical in all respects with that of those cases in which there was no known previous acute stage. The explanation of the occurrence of this late stage without a history of previous acute nephritis lies in the fact that an acute nephritis may be so mild that it is altogether missed. Lyttle (1933) performed the sediment count on 16 patients who had had scarlet fever two to eight weeks previously, with no clinical evidence of nephritis, and found abnormal numbers of casts, red blood cells, and albumin in the urine of 14. De Wesselow, Goadby, and Derry (1935) examined the urine in 354 cases of acute tonsillitis for three weeks after the onset of the infection, and found three undoubted cases of diffuse nephritis, and other cases with abnormalities of the urine which would otherwise have passed unrecognized.

Apart altogether from such special investigations, it is well known how many cases of nephritis are discovered for the first time in the latent stage of the disease. It has been pointed out by several workers, especially Lyttle and Rosenberg (1929), Addis (1931), Bierman (1937), Snoke (1937), and Bell (1938) that the latent stage is completely symptomless. It is therefore often missed, and it is easy to understand how nephritis may have existed for several years before it is seen in the degenerative or terminal stage.

We thought that it would be useful to attempt to fit into one scheme, such as that of Addis, the various names given to nephritis. This has been done in Table II. It will be seen that the table takes into consideration the differences of opinion which exist about the meaning of certain terms such as 'exudative nephritis' and 'haemorrhagic nephritis'. For the purposes of the table the various stages are numbered, as follows: Stage I, the acute stage; Stage II, the latent stage; Stage III, the degenerative stage; Stage IV, the terminal stage.

Having suggested that all the various classifications of nephritis may fit into one scheme, it now remains to decide whether or not it is necessary to distinguish clinically acute focal from acute diffuse nephritis. To do this we shall have to study many of the various aspects of nephritis in childhood, the aetiology, symptomatology, and other features, in order that a complete comparison of the various manifestations in the two types may be obtained. At the same time, we shall take the opportunity of reviewing the literature and suggesting reasons for the divergences of opinion revealed.

*Acute focal glomerulonephritis.* Scheidemandel (1913) was apparently the first to draw attention to this condition. Volhard and Fahr (1914)



subsequently described it in detail. According to their definition acute focal nephritis is a symptomless haematuria, occurring at the height of an acute infection, without oedema, nitrogen retention, hypertension, or reduction in urinary volume, and with a uniformly good prognosis. They say that only in very exceptional cases is there slight reduction in urinary volume, or very

TABLE II

*The Classification of Nephritis.*

Excluded from the table are: Acute interstitial nephritis (pathological entity); Acute embolic nephritis (in infective endocarditis); Acute pyelonephritis (acute pyelitis of infants).

Terms in current use.	Suggested meaning.
Acute focal nephritis	Nephritis, Stage I, without oedema
„ haemorrhagic focal nephritis	„ „ „ „
„ focal glomerulonephritis	„ „ „ „
„ haemorrhagic nephritis	Nephritis, Stage I, with or without oedema, according to the person using the term
„ haematuric nephritis	„ „ „ „
„ post-infectious haemorrhagic nephritis	„ „ „ „
„ diffuse nephritis	Nephritis, Stage I, usually with oedema
„ diffuse glomerulonephritis	„ „ „ „
„ glomerulonephritis	„ „ „ „
„ glomerulotubular nephritis	1. Nephritis, Stage I, with oedema, or 2. Nephritis, Stage III, according to the person using the term
„ exudative nephritis	„ „ „ „
„ parenchymatous nephritis	„ „ „ „
„ diffuse tubular nephritis	„ „ „ „
„ oedematous nephritis	„ „ „ „
„ mixed types	„ „ „ „
„ hydraemic nephritis	Nephritis, Stage III
„ tubular nephritis	„ „
„ desquamative nephritis	„ „
Subacute non-haemorrhagic nephritis	„ „
„ parenchymatous nephritis	„ „
„ glomerulonephritis	„ „
„ glomerulotubular nephritis	„ „
„ diffuse nephritis	„ „
Chronic subacute nephritis	„ „
Nephrotic nephritis	„ „
Chronic parenchymatous nephritis	„ „
„ mixed nephritis	„ „
Nephrosis	Nephritis, Stage III (wrongly) or true nephrosis
Chronic glomerulonephritis	Nephritis, Stage II, III or IV, according to the person using the term
„ interstitial nephritis	Nephritis, Stage IV
Azotaemic nephritis	Any stage of nephritis in which there is nitrogen retention

slight nitrogen retention. Only very rarely does a case progress to chronic nephritis. Such is the picture given by Volhard and Fahr. The same description of the disease is given by other writers who discuss the condition (Stone, 1936; Baehr, 1926; Cockburn, 1935; Still, 1927; Fishberg, 1934; Hadfield and Garrod, 1938; Boyd, 1927; Hill, 1919). Weiss (1927) goes so far as to call it a 'mere incident in the course of an infectious disease'.

The pathology of the disease is discussed by Gray (1933). Unfortunately,

the clinical picture of the cases he studies does not fit in with the picture given by Volhard and Fahr (1914), and we do not feel, therefore, that further reference need be made to Gray's paper. As for nitrogen retention, Fishberg (1934) states that it never occurs in focal nephritis. Sheldon (1938) states that very rarely the blood-urea may rise as high as 70 mg. per 100 c.c. Volhard and Fahr (1914) state that very rarely it may be as high as 80 mg. per 100 c.c.

It is implied that the diagnosis is easy, and that the condition can be readily distinguished from the diffuse type. Volhard and Fahr state that only exceptionally is the distinction difficult. Still (1927) states that in the first few days of the illness no one can say to which type of nephritis the case belongs. Ball and Evans (1932), however, point out that the differential diagnosis is often impossible. Bell (1935) states that it is highly probable that mild acute diffuse nephritis is often diagnosed clinically as focal nephritis, and that in his opinion the desirability of distinguishing between the two conditions is dubious. The consensus of opinion is that the prognosis is excellent. Volhard and Fahr state that only very rarely does a case go on to chronic nephritis. Hill (1919), however, prefers to regard acute focal nephritis as a serious condition, though elsewhere he gives it a good prognosis. The other authors mentioned, except Addis (1931), all agree as to the excellence of the prognosis.

It is therefore surprising that on reading the literature, which covered some hundred communications, no paper, other than that by Addis, was found to give a record of the follow-up of these cases. Addis, unfortunately, does not give figures which show the exact prognosis of the condition. Volhard and Fahr omit to give figures to support their contention about the excellence of the prognosis. They do not say how many cases they have followed up, for how long they have followed them, or what tests they have used to determine the condition of the kidney on re-examination. Addis (1925, 1931), however, by the sediment count, has followed these cases through from the acute attack to the *post mortem*. He states:

'It is quite generally supposed that there is a focal glomerulonephritis which should be distinguished from diffuse glomerulonephritis because it has a distinctly different pathogenesis, prognosis, and pathology. Clinically, it is a presumably benign disease, without hypertension or arteriosclerosis, whose only clinical manifestation is a slight continuous haematuria. But when these patients are watched for years and it is observed that in some the renal lesion heals, and in others, though often very slowly, there is in the end the gradual development of hypertension, arteriosclerosis, and ultimately of uraemia, and when the pathologist fails to find any essential difference between these kidneys and those of other patients in whom the initial clinical stage was observed, it becomes simpler to suppose that this focal glomerulonephritis is really only the latent stage of haemorrhagic Bright's disease.'

It is almost universally accepted that in the distinction of the focal from

the diffuse type the most important single diagnostic criterion is the presence or absence of oedema. Most writers agree that there is *never* oedema in acute focal nephritis, and that there is oedema in the diffuse type. This, we feel, is the best single criterion we can adopt for the study of the cases (though we shall subsequently deal with the other criteria used for the diagnosis of the condition), and we have accordingly divided all our cases into three groups for the entire study.

Group I. Cases with no oedema in the acute stage.

Group II. Cases with no oedema other than puffiness of the eyelids.

Group III. Cases with generalized oedema.

For statistical reasons we have referred only to the 301 cases seen by us in the acute stage, except in certain special tables, such as that showing the sex incidence in which we have included cases seen for the first time in later stages of the disease. Group II has been separated from the other groups because of the difficulty of deciding whether or not these cases show oedema, for as Sheldon (1938) points out, many children have puffiness of the eyelids without having nephritis. Other doubtful cases with generalized oedema, in which it was uncertain whether the disease was in the acute or degenerative stage, were excluded from the series.

The following is the analysis of the cases to be described :

	Group I.	Group II.	Group III.	Total.
Cases seen in acute stage	139	92	70	301
Not seen in acute stage	8	9	13	30
Seen first in degenerative stage (no known acute attack)	—	—	—	24
Unclassified				10
Total				365

The study of the age and sex incidence of acute nephritis does not reveal anything of note. The greatest incidence of nephritis in this hospital seems to fall into the age group five to six years. It will be seen from Table IV that there were 184 males in the series and 181 females. Others<sup>2</sup> have stated that the condition is commoner in males than females. Some writers<sup>3</sup> have discussed hereditary and familial factors in acute nephritis. It may be noted that 30 of our series had a family history of nephritis; this figure is necessarily based on the statement made by the parents, and may or may not be accurate.

Table VI shows that 77 per cent. of all cases were due to infections of the ear, nose, and throat. The aetiological factors have been studied by numerous writers<sup>4</sup> and the figures given in their papers tally closely with those given in

<sup>2</sup> Archibald, 1937; Greenwood, 1927; Griffith and Mitchell, 1937; Lyttle and Rosenberg, 1929; Snoke, 1937; Stone, 1936.

<sup>3</sup> Allison, 1925; Eason and Smith, 1924; English, 1936; Erstene and Robb, 1931; Hill, 1919; Hurst, 1923; Snoke, 1937.

<sup>4</sup> Allison, 1925; Ball and Evans, 1932; Blackfan, 1926; Boyd, 1922; Cockburn, 1935; Findlay, 1928; Fishberg, 1934; Hill, 1919; Hutinel, 1910; Longcope, 1927; Lyttle and Rosenberg, 1929; McLanahan, 1912; Nauheimer, 1911; Osman, 1925; Paterson and Wyllie, 1926; Phillips, 1910.

TABLE III

*Aetiology. Age Incidence in Acute Nephritis.*

	Total cases 331 *											
Ages (in years)	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12
Group I	1	3	16	23	15	27	24	10	10	11	5	4
Group II	—	—	14	14	17	15	12	13	6	8	2	—
Group III	3	5	11	5	11	11	7	4	6	6	4	8
Total	4	8	41	42	43	53	43	27	22	25	11	12

TABLE IV

*Sex Incidence of 365 Cases of Nephritis.*

	Male.	Female.
Group I	66	81
Group II	65	36
Group III	36	47
Unclassified	17	17
	<u>184</u>	<u>181</u>

TABLE V

*Analysis of Season in which Cases of Acute Nephritis Commenced.*

	Total cases 331			
	Jan.-March.	April-June.	July-Sept.	Oct.-Dec.
Group I	36	52	26	39
Group II	16	22	28	40
Group III	13	18	25	16
	<u>65</u>	<u>92</u>	<u>79</u>	<u>95</u>

TABLE VI

*Precipitating Infections in Acute Nephritis.*

Infection.	Group I	Group II	Group III
	%	%	%
Tonsillitis, pharyngitis	41	40	38
Otitis*	14	13	10
Acute cervical adenitis	9	6	6
Coryza	6	8	12
Tonsillectomy	5	5	5
Scarlet fever	4	4	2
Skin conditions	3	4	3
Miscellaneous	5	2	7
Unknown	13	18	17
Total upper respiratory tract infections	79	76	73

\* Otitis was very frequently associated with tonsillitis. The figure given here for otitis refers to cases in which there was not an associated acute tonsillitis.

Under the heading 'miscellaneous' are included empyema, thyroid abscess, purpura, pneumonia, mumps, extraction of teeth, chicken-pox, influenza, antritis, diphtheria, septicaemia, and osteomyelitis.

Table VI. McPhee and Kaye (1932), however, state the surprising fact that in their series of 90 patients in only nine could the aetiological factor be ascertained. Most of the other writers mentioned above gave definite aetiological factors in 70 to 90 per cent. of their cases. The high incidence of infection by the haemolytic streptococcus is given in many of the papers mentioned.

TABLE VII

*Symptomatology. Commonest Symptoms before Admission to Hospital. Acute Stage only.*

Symptoms.	Group I %	Group II %	Group III %
Puffiness of the eyelids without other oedema	—	79	—
Oedema	—	—	87
Haematuria	75	74	63
Vomiting	32	35	43
Frequency of micturition	15	17	16
Abdominal pain	14	18	23
Headache	13	17	19
Dysuria	8	7	17
Constipation (recent)	8	7	10
Oliguria	6	0	3
Backache	4	11	4
Enuresis	4	0	0
Drowsiness	4	9	13
Thirst	4	8	4
Symptomless apart from haematuria and/or oedema	23	23	17

Longcope (1927) found this organism in 81·2 per cent. of his cases. Boyd (1922) found the haemolytic streptococcus in three out of five blood cultures in cases of the 'focal' type, and others (Scheidemandel, 1913; Fishberg, 1934) have found the organism in the urine. It will be seen that in the aetiological factors there is no feature which helps us to distinguish the two types of nephritis.

*Symptomatology.* Great stress is laid on the differences in symptomatology in the two types of nephritis, focal and diffuse, by practically all writers on the subject. Almost all are agreed that acute focal nephritis is a practically symptomless disease. Fishberg (1934), for example, states that the symptoms are little more than the passage of blood, albumin, and casts in the urine. He adds: 'In the vast majority of cases focal nephritis is merely an incident in the course of an infectious disease, not influencing the course of the primary malady, and discovered only as a result of the urinary abnormalities.' Volhard and Fahr (1914) state that headaches and vomiting do not occur in this condition.

The idea that acute focal nephritis is such a monosymptomatic condition is erroneous, as is shown by Table VII. The table is naturally incomplete, as it is prepared for the most part from old In-patient notes, and not all the histories were very carefully taken. It is obvious that if a careful history were to have been taken in every case, many more symptoms would be added

to the list, but for purposes of comparison between the groups the table is of value. It will be seen that vomiting occurred in one-third of the cases in Group I, and that approximately one out of seven had headaches, acute abdominal pain, or frequency of micturition. On comparing these figures with those of Group III, it is seen that the symptoms mentioned are only slightly more frequent in the latter group. In Group I approximately 28 per cent. are symptomless apart from haematuria, while in Group III 17 per cent. are similarly symptomless. It will also be noticed that the order of frequency of the symptoms is very closely similar in the two groups. It will be noted that certain symptoms not commonly mentioned in text-books are frequently present—severe abdominal pain (in one case resulting in a laparotomy), frequency of micturition, dysuria, and enuresis, the last, presumably, being due to the frequency. It appears, in short, that in the symptomatology we have no criterion for the distinction of the two types of nephritis.

*Time-interval between the acute infection and the onset of acute nephritis.* All writers on the subject are agreed that acute focal nephritis occurs at the height of the acute infection, whereas the diffuse nephritis occurs at an interval of one to three or four weeks after the infection, usually long after the causative illness has subsided. A possible exception is given by Hill (1919), who, discussing 'acute haemorrhagic nephritis', states that 'nephritis is most likely to occur several days or even a couple of weeks after the onset of acute tonsillitis and is likely to be of the pure haemorrhagic type without oedema', thus suggesting that acute focal nephritis may occur not only at the height of the infectious process, but a fortnight later. Addis (1931), in an excellent paper in which he prefers to talk about one acute nephritis and not to distinguish the focal type from the diffuse, gives the following table:

Days from onset of preceding illness.	Percentage incidence.
0 to 6	27
7 to 12	27
13 to 18	33
19 to 24	13

Ball and Evans (1932) state that the interval between the acute infection and the onset of diffuse nephritis is *often* seven to fourteen days, implying, presumably, that the interval may be shorter or longer than this. There appear to be no other references to the fact that diffuse nephritis may occur at the height of the infection.

We have found the time-interval in the majority of cases to be very difficult to estimate. In most cases the probable date of onset of the nephritis can be determined only by accepting the mother's statement about the day on which haematuria was first noticed. In many cases (14 per cent. of our series) the infection causing the condition is unknown, or at least unknown to the parents (as in 16 per cent. of our cases) and found only by the physician. In 13 per cent. of our cases there was a 'double' infection, tonsillitis followed by otitis media and then by nephritis, or an otitis associated with a septic skin condition. In 10 per cent. of our cases the acute nephritis



occurred during the course of a protracted illness, such as mastoiditis or empyema, without the intervention of any acute exacerbation from which the onset of the nephritis could be dated. It will be seen, however, in Table VIII, that in those cases in which it is possible to estimate this time-interval with a reasonable degree of accuracy, there is no difference in the three

TABLE VIII

*Time-interval between Infection and Nephritis.*

	Group I Total cases 139.	Group II Total cases 42.	Group III Total cases 70.
Time-interval 0 to 6 days	43 (31 %)	25 (27 %)	24 (34 %)
Time-interval 7 to 14 days	9 } (15 %)	13 } (16 %)	6 } (15 %)
Time-interval 14 to 21 days	11 }	2 }	4 }
Time-interval indeterminate because:			
(a) Causative infection was unknown to parents	30 (21 %)	10 (11 %)	9 (13 %)
(b) The nephritis occurred during the course of a protracted infection	15 (11 %)	11 (12 %)	4 (6 %)
(c) There was a 'double' infection, one possible causative infection being followed by or associated with another	12 (8 %)	14 (15 %)	8 (11 %)
(d) No causative infection was found, and for other reasons	19 (14 %)	17 (19 %)	15 (21 %)

groups. It is found that 31 per cent. of cases in Group I started 0 to 6 days after the onset of the infection (therefore presumably at or very near the height of the infection), compared with 34 per cent. in Group III, and that 15 per cent. of the cases in each of these groups commenced from seven to twenty-one days after the onset of the acute infection. It seems, therefore, that the interval between infection and nephritis is not an important distinguishing feature between focal and diffuse glomerulonephritis.

*Nitrogen retention.* It has already been pointed out that practically all writers are unanimous in stating that only exceptionally does nitrogen retention occur in focal nephritis. Baehr (1926), for instance, states that one can eliminate focal nephritis at once if any nitrogen retention occurs, but most writers hold that nitrogen retention is frequent in diffuse nephritis. Unfortunately, apart from the paper by Rennie (1935), figures are not given which show the level of the blood-urea in focal nephritis, or, if they are given (Hill, 1917) no note is made about the day, in relation to the time of onset of the disease, on which the blood-urea was estimated.

Rennie reviewed the question of azotaemia in Bright's disease in 1935, but most of his references deal with cases of diffuse nephritis. Lyttle and Rosenberg (1929) mention the incidence of nitrogen retention in diffuse cases. Crawford (1924) mentions the high incidence of nitrogen retention in the acute nephritis of children, but does not separate the different types of acute nephritis, and includes late cases in his series. Other references deal mainly with adults. Rennie, however, gives a useful table based on the non-protein nitrogen records of 98 children :



Oedema.	Cases.	Non-protein nitrogen.	
		Average.	Range.
0	12	60.0	20.6 to 190.0
+ -	29	49.6	19.1 to 113.0
+	27	55.4	22.4 to 176.5
++	30	63.4	17.0 to 280.0

He also pointed out a phenomenon which others have not mentioned, namely, the rapid return of the figure to normal. He gives a graph, based on 220 observations on the 98 cases, which shows the very much greater incidence of high readings at an early date of the disease than at a later date. It will be seen that in his series of 12 cases without oedema there was nitrogen retention of considerable degree.

It is difficult to understand how it comes about that nitrogen retention is considered to occur in the diffuse type and not in the focal type. Table IX shows that actually nitrogen retention occurs very frequently in Group I and that a high degree of retention is rather more frequent in Group I than in Group III. The blood-urea was estimated in 74 cases in Group I before the fortieth day of the disease, similarly in 60 cases in Group II, and 47 cases in Group III. It will be seen that in 49 per cent. in Group I, 47 per cent. in Group II, and 43 per cent. in Group III, there was a blood-urea of over 50 mg. per 100 c.c., and that in 17 per cent. of Group I, 8 per cent. of Group II, and 15 per cent. of Group III the blood-urea was over 100 mg. per 100 c.c.

In Table IX the figures for blood-urea are based on the first estimation if more than one estimation was made, and are grouped according to the interval between the onset of the nephritis and the day of the blood-urea estimation. It is necessary to stress this point, as the level of the blood-urea alters very rapidly. Table X shows the rapid drop in the figure in 10 cases in which there was a high degree of nitrogen retention.

This rapid fall starts early in the disease, and it can be understood that a normal reading taken, say, on the seventh day of the disease can be deceptive unless it is remembered how rapidly the nitrogen retention disappears. In 80 per cent. of our cases in which a second estimation was made within a week of the first, the second figure was the lower one. The same applies to the urinary findings. In only five cases in Group I, one case in Group II, and five cases in Group III, was the quantity of albumin in the urine increasing in successive specimens on admission. The figures suggest that the kidney in acute nephritis receives a sudden severe knock-out blow, and rapidly recovers from it, so that within a week there may be no evidence of nitrogen retention in a case which at the onset had a very considerable degree of retention, and only a small amount of albumin and blood in a case which at the onset exhibited a very great deal of both. Some of our figures, based on daily estimations of the blood-urea, indicate that in some cases it is a matter of hours and not days before the nitrogen retention reaches its maximum and then rapidly falls. It may be argued that it was only in the severe cases that the blood-urea was estimated. It must be pointed out,

however, that the blood-urea was raised in 57 per cent. of the cases in which the onset was symptomless apart from the haematuria. In any case, the comparison between the three groups is a true one.

There is no relation between the age of the children and the degree of nitrogen retention; the same high degree of retention can occur equally at any age. A blood-urea of 343 mg. per 100 c.c. was recorded in a child of

TABLE IX

*Study of Nitrogen Retention (Indicated by Height of Blood-urea) at Different Time-intervals after Onset of Acute Nephritis.*

If more than one blood-urea estimation was done on any one patient, the first estimation alone is used for this Table.

Group.	Duration of nephritis.	Number of cases.	Normal 10 to 40 mg. %	40 to 50 mg. %	50 to 60 mg. %	60 to 80 mg. %	80 to 100 mg. %	100 to 200 mg. %	Over 200 mg. %
Group I	0 to 5 days	20	10	1	3	2	0	1	3
	5 to 10 days	26	5	6	3	4	2	4	2
	10 to 20 days	19	4	5	3	3	1	3	0
	20 to 40 days	9	7	0	0	1	1	0	0
Total		74	26	12	9	10	4	8	5
Group II	0 to 5 days	17	6	3	1	2	1	1	3
	5 to 10 days	16	3	2	2	6	2	1	0
	10 to 20 days	17	9	1	5	1	1	0	0
	20 to 40 days	10	7	1	2	0	0	0	0
Total		60	25	7	10	9	4	2	3
Group III	0 to 5 days	4	0	0	2	0	0	2	0
	5 to 10 days	17	6	3	4	1	1	2	0
	10 to 20 days	13	8	2	1	2	0	0	0
	20 to 40 days	13	7	1	1	0	1	3	0
Total		47	21	6	8	3	2	7	0

TABLE X

*The Rapidity of the Fall of the Blood-urea to Normal.*

Case 1	Blood-urea of 345 mg. per cent. fell to 35 mg. per cent. in 11 days
" 2	" 323 " " 41 " 19 "
" 3	" 253 " " 52 " 9 "
" 4	" 204 " " 35 " 7 "
" 5	" 192 " " 33 " 7 "
" 6	" 176 " " 41 " 4 "
" 7	" 184 " " 48 " 10 "
" 8	" 149 " " 41 " 4 "
" 9	" 137 " " 27 " 11 "
" 10	" 135 " " 32 " 7 "

two years who survived. The relation of blood-urea to symptoms is shown in table XI, in which, if more than one estimation was made, the highest recorded figure is the one shown. Vomiting is the commonest symptom; convulsions, seen in several cases of uraemia in later stages of nephritis, were seen in only two of the acute cases. Unfortunately the histories of some of these children are not always complete, and it is probable that many more children than those mentioned had symptoms such as vomiting and drowsiness.

The immediate mortality of these cases with marked nitrogen retention is not high. There were five deaths in the 30 children whose blood-urea was above 100 mg. per 100 c.c., and it is probable that many others had a similarly high degree of nitrogen retention which was never recognized, because an estimation was not done sufficiently early. We have reached the conclusion,

TABLE XI

*Relation of High Blood-urea to Symptoms, in Acute Cases only*

	Height of blood-urea in acute attack. (Highest figure recorded in mg. %).	Total cases.	Vomiting.	Drowsiness.	Convulsions.	Died.
Group I	100 to 200	11	7	2	—	1
	200 to 300	2	2	—	—	1
	over 300	3	2	2	2	1
Total		16	11	4	2	3
Group II	100 to 200	2	1	—	—	—
	200 to 300	1	1	1	—	—
	over 300	2	2	2	—	—
Total		5	4	3	—	—
Group III	100 to 200	5	2	—	—	1
	200 to 300	4	4	3	—	1
	over 300	—	—	—	—	—
Total		9	6	3	—	2

therefore, that nitrogen retention is just as common in Group I as it is in Group III. Nitrogen retention, therefore, is not a feature which distinguishes the two types of nephritis.

*Hypertension in acute nephritis.* We do not propose to present figures which show the degree of hypertension which may occur in acute nephritis of any of the three types, though we may say that in 11 cases in Group I a systolic reading of over 130 mm. of Hg was recorded. Blood-pressure estimations in children need to be taken with great care because of the importance of emotional factors. The readings which we have were taken by various doctors and students, and the personal factor is therefore so great that our figures are of doubtful value.

*Urinary output in acute nephritis.* Here again our figures are not very useful, partly because the common occurrence of enuresis in children makes the recorded urinary volumes frequently incomplete. In any case, nephritis so frequently occurs in an acute febrile illness that oliguria is to be expected because of the fever, a fact pointed out by Volhard and Fahr (1914). The following is a summary of our figures:

	Group I.	Group II.	Group III.
Oliguria noted by parents	9	11	12
Marked oliguria noted in hospital	12	9	7
Normal output in hospital	73	61	35
Insufficient records	45	11	16
Total cases	139	92	70

By marked oliguria is indicated an output of less than 12 oz. per diem.

*Oedema in acute nephritis.* It has already been stated that most authorities are agreed that in focal nephritis there is no oedema, though some grant that there may be some puffiness of the eyelids. All give the presence or absence of oedema as a basic criterion for the distinction of focal nephritis from the diffuse type. In this connexion we give two sets of figures. One shows the difficulty with regard to puffiness as a sign of oedema, the other a difficulty which may arise in the diagnosis of cases which develop oedema only some time after the onset of nephritis.

	Group II.
Puffiness of eyelids seen by parents, not seen on admission	25
Puffiness of eyelids seen on admission, not noted by parents	18
Puffiness of eyelids noted by parents and seen in hospital	49
Total	92

The figures suggest that, as a symptom which is obtained from the parents, puffiness of the eyelids is not of great value, or else that it is evanescent and in more than a quarter of the cases has disappeared before admission. It will be seen that if puffiness of the eyelids is to be taken as a sign of oedema, the absence of oedema being a basic criterion for the diagnosis of focal nephritis, the distinction between the two types of nephritis on these grounds is likely to be difficult. Another difficulty is shown by the fact that in 24 (30 per cent.) of the cases in Group II haematuria was noticed more than a week before the puffiness of the eyelids. This suggests that in many cases a diagnosis of focal nephritis will be made, only to be changed to one of diffuse nephritis when oedema later manifests itself.

*Exacerbation of the nephritis after tonsillectomy.* The whole question of the relation of tonsillectomy to nephritis is discussed in another paper by one of us (Illingworth, 1939).

Many authors have stated that it is characteristic of the focal type of nephritis that tonsillectomy is followed by an exacerbation of the renal condition. Scheidemandel (1913), for instance, is quoted as saying that such an exacerbation 'is a striking therapeutic criterion of differential diagnostic value in focal nephritis', and that it rarely occurs in the diffuse type. Our figures do not confirm this view. Tonsillectomy was performed in 119 of our cases as a therapeutic measure in acute nephritis; in 94 of these cases there were known signs of activity of the disease process, and there were exacerbations of the process in 28 cases. The following figures show the frequency of exacerbations in the three groups:

	Group I.	Group II.	Group III.	Total.
Total number of cases operated upon	61	36	22	119
Total cases showing known activity of renal lesion at time of operation	47	26	21	94
Exacerbation resulting from tonsillectomy	11	7	10	28

Thus another of the suggested criteria for the diagnosis of focal nephritis is shown to be unreliable.

*The prognosis of acute nephritis.* The literature concerning the prognosis

of focal nephritis has already been discussed. A great deal more has been written about the prognosis of acute diffuse nephritis. Some authors in addition discuss the prognosis of acute nephritis without distinguishing the focal from the diffuse type. Most writers give acute nephritis in childhood a good prognosis. Hutchison (1931) says that 'the patient almost never dies in an attack, and in the majority the condition clears up very well'. Thurstfield and Paterson (1934) state that a complete recovery occurs in mild cases of acute nephritis. Blackfan (1926) states that complete recovery takes place in the majority of cases; 21 out of his series of 24 recovered completely, and three died of uraemia, but it is uncertain what he means by complete recovery. Thomson and Findlay (1933) say that the 'prognosis is eminently favourable. Few cases pass into the subacute parenchymatous stage. Of 25 cases of acute nephritis discharged in a year from a hospital in Glasgow 20 cases were dismissed completely cured.' Tallerman (1932) followed cases up for one and a half to three and a half years and gave a recovery rate of 66.6 per cent. Cockburn (1935) followed 41 patients for periods varying from three months to seven years and found abnormal urine in two only. Yampolsky (1937) says that the usual course of the disease is complete recovery. He apparently based this statement on the condition of the patients on discharge. Ernberg (1911) examined 40 adults who had had nephritis, in most cases before the age of 15 years, and found the urine to be normal in all of them. Rosenfeld and von Rechtenstamm (1930) examined 94 persons who had had acute scarlatinal nephritis several years previously and found that none had severe chronic nephritis. Lyttle and Rosenberg (1929) followed up 58 cases and found that 15.5 per cent. became chronic; they gave a total mortality of 11.1 per cent. Allison (1925) followed 12 cases for periods varying from nine months to one year and found no evidence of kidney disease in any. Boyle, Aldrich, Frank, and Borowsky (1937) examined the urine of patients one and a half to eight years after acute nephritis and found it normal in all cases. Hansborg (1924) examined 284 children from one to ten years after an attack of acute nephritis and could find no abnormality in 259 of them. James (1921) examined 67 children from three months to fifteen years after acute nephritis; 13.3 per cent. were in the chronic stage. Boyd (1927) examined 50 patients from two to five years after the acute attack; 72 per cent. were found to be normal, 12 per cent. had died, 16 per cent. were in the chronic stage. Guild (1931) in a careful follow-up found that 26.5 per cent. of 34 cases had albumin in the urine on re-examination. Aldrich (1930) followed up 129 cases of acute nephritis; all were 'entirely well' when seen by him. McPhee and Kaye (1932) examined 48 cases some years after the acute attack and found that none had progressed to chronic nephritis. Other papers giving a good prognosis are those by Hill (1919) and Greenwood (1927). Stone (1936) gives a mortality in the acute stage of 5 to 10 per cent., and progress to the chronic stage in another 10 per cent.

On the other hand, Bell (1935) followed 72 cases for one to nine years; 36 per cent. recovered, 19.4 per cent. were latent, 3.9 per cent. active or



terminal, and 30.5 per cent. died. These figures probably refer largely to adults. Snoke (1937) examined 154 patients thoroughly over many years and found that 37 per cent. were healed, 41.5 per cent. were active, and 21.4 per cent. had died; he predicted an eventual mortality of about 40 per cent. Still (1927) referring to the diffuse type, says that 'it is the minority of cases which ever make a complete recovery'. Holt (1897) said that acute nephritis in childhood not infrequently leads to chronic nephritis, and warned against a uniformly good prognosis. Bierman (1937) followed 35 cases for one to five years and found that less than 40 per cent. gave satisfactory evidence of complete recovery. He, like Lyttle and Rosenberg (1929) and Bell (1938), was impressed by the apparent good health of children in the stage of latent and chronic nephritis. Osman (1925) followed 56 cases for one and a half to twenty-two years; 64 per cent. recovered, 35.7 per cent. showed evidence of renal dysfunction. Hill (1919) states that acute nephritis of either type should always be regarded as a serious disease. Smellie (1926) examined 16 cases at least ten years after acute nephritis; none had symptoms of the disease, but only five (31 per cent.) had normal blood-pressure, blood-urea, and concentration tests. Wessler (1914) examined by auscultation and orthodiagraphy the hearts of children who had had nephritis, and found that all his eight cases showed hypertrophy of the left ventricle. Wyllie and Moncrieff (1926) examined 14 cases four months to three years after the attack; only three cases (21 per cent.) were found to have normal urine. They consider, however, that albumin, in the absence of red blood-cells, is of no importance. Paterson and Wyllie (1926) re-examined 22 cases of 'acute parenchymatous nephritis' and 27 cases of 'acute haemorrhagic nephritis', three and a half years after the attack. In the parenchymatous group 6 died, 11 had abnormal urine, and 5 recovered; in the haemorrhagic group 1 died of meningitis, 14 had abnormal urine, 12 recovered; a total of 17 (34 per cent.) out of the 49 cases had recovered completely.

There is a similar divergence of opinion about the factors which influence prognosis. Griffith and Mitchell (1937) state that the younger the child the worse the prognosis. Guild (1931) considers that the reverse is the case. Snoke (1937) thinks that age has no effect at all on prognosis. Thomson and Findlay (1933) state that an acute onset is followed by rapid recovery. Berglund and Medes (1935) think that the severity of the original attack has no effect on the prognosis. Guild (1931), Osman (1925), Weiss (1937), and Tallerman (1932) agree with this opinion. Addis (1931), though admitting that very mild cases may go on to chronic nephritis, thinks that cases with an intense initial stage seem to have a worse prognosis than the milder ones.

Tallerman (1932), Lyttle and Rosenberg (1929), Parsons (1926), Crawford (1924), and Snoke (1937) all agree that nitrogen retention in the acute stage has no effect on ultimate prognosis. Griffith and Mitchell (1937) think that nitrogen retention is of bad prognostic significance. Snoke (1937) states that there is no connexion between the intensity of the preceding infection and the outcome. Berglund and Medes (1935) consider that the severity of

the acute infection does affect the prognosis, and quote Winkenwerder's work which shows that if a severe acute streptococcal infection precedes the nephritis the prognosis is better than if a lower-grade infection is the cause of the nephritis. Aldrich (1930) and Ball and Evans (1932) say that the prognosis is better if there is a known cause for the nephritis.

Stone (1936), Archibald (1937), Moorhead (1928), Berglund and Medes (1935), Guild (1931), Boyd (1922), and others point out that prolongation of the acute stage is of serious prognostic significance. It has already been stated that authors are agreed, with very few exceptions, that acute focal nephritis has a better prognosis than the diffuse type. The literature on the relationship between tonsillectomy and prognosis will be discussed in a separate paper.

It seems difficult to understand why there should be so much diversity of opinion as to the prognosis of acute nephritis. The reasons we suggest are:

1. *Failure to recognize the latent stage.* Snoke (1937) says that the almost universal failure to recognize the latent stage is chiefly responsible for the divergent views on the classification of nephritis and for the conflicting statistics with regard to prognosis and healing in general. He says that no patient can be considered to be healed until repeated quantitative examinations of concentrated urine have given the patient a clean bill of health. The children in the latent stage are almost always perfectly well and free from symptoms. Apart from occasional headaches in those with markedly raised blood-pressures, all our cases were entirely symptomless in this stage. Only careful examination of the urinary deposit, with a determination of the blood-pressure, may reveal the true state of the kidney. The latent stage may last for a considerable time. Bell (1938) in a recent paper mentions a case in which this stage lasted for 24 years.

2. *Failure to examine the urinary deposit.* Careful microscopy of a centrifuged deposit is essential for diagnosis. Snoke and others in America employ the more accurate method of the sediment count in order to judge the progress of the patient. Many of the papers which give a uniformly good prognosis give no mention of whether the deposit was examined. Many writers have given a uniformly good prognosis because the patients were 'discharged cured'. In these papers there is no note about the urinary deposit, and the possibility of a latent stage following on the acute is not mentioned.

3. *Failure to record the blood-pressure.* It will be shown that this is often raised in the latent stage without discoverable urinary abnormality.

4. *Disregard of small amounts of albumin* in the urine in the absence of excess of red blood-cells. Several writers say that such albuminuria is of no significance. Continuous very slight albuminuria is often the only indication of latency, and only at intervals are there red blood-cells in excess in the urine. Many of our cases had a raised blood-pressure, a trace of albumin, and no red blood-cells in the urine. The amount of albumin in the urine in the latent stage is always or nearly always slight, usually 10 to 20 mg. per



100 c.c. Others have disregarded albuminuria which is orthostatic. Russell (1925), however, showed that the albuminuria of nephritis is orthostatic in both the acute and the latent stage. He showed that 26.5 per cent. of cases convalescent from scarlet fever had orthostatic albuminuria, compared with 3.1 per cent. of cases convalescent from other illnesses. Fishberg (1934) also points out that the albuminuria of nephritis is orthostatic, and says that the differentiation of benign albuminuria from organic renal disease is often a matter of great difficulty requiring a long period of observation. Therefore, because the albuminuria in a patient who has already had one attack of acute nephritis is orthostatic in character, it is not justifiable to assume that the albuminuria is benign.

5. *The inclusion of cases seen first in the latent or degenerative stage.* It has already been shown that many cases of the degenerative stage of nephritis have been called acute nephritis, acute tubular nephritis, &c., and confused with cases truly in the acute stage. Many have stated that cases with marked oedema, with an insidious onset of oedema, with no known precipitating cause, or with very little blood in the urine, have a worse prognosis than cases with much haematuria, with a known causative infection, and having a sudden onset. This is probably often due to the fact that the former are cases of the degenerative stage, and not acute nephritis at all.

6. *Too short a period of observation.* Cases should be followed for many years before a true statement can be made about the condition of the kidney. The majority of series in the literature have been followed up for less than four years.

7. *Undue reliance on renal function tests.* In the latent stage these tests usually show no abnormality at all. Only when more than two-thirds of the kidney have been destroyed do most tests show any abnormality (Harrison, 1930).

8. *Reliance on clinical impressions rather than on thorough and adequate follow up of cases for a sufficient number of years after the onset of the nephritis.*

#### *The Present Series*

(i) *Mortality.* In the acute stage of the disease 14 cases died, four in Group I, two in Group II, and eight in Group III. There is therefore a higher immediate mortality in the presence of oedema than in its absence. Four of these cases had an acute septicaemia, and in one the nephritis was a complication of a chronic empyema. Post-mortem examination performed on 10 of these cases confirmed the diagnosis of acute nephritis. It may be noted that in only one of these 14 cases was it possible to state the time-interval between the causative infection and the onset of the nephritis. Four cases seen under the age of 1½ years died during the first manifestation of the disease, but we are not certain whether these cases were in the acute or degenerative stage, and they have therefore been excluded from the series. Six out of the eight fatal cases in which a series of blood-urea estimations was performed had a rising blood-urea before death, such rise being

a sign of serious prognostic significance. Four cases, which survived the acute attack, are known to have died subsequently of chronic nephritis. Two of these cases belonged to Group I, and two to Group III. It must be pointed out, however, that out of 350 patients to whom we wrote for purposes of re-examination, only 94 responded, so that we are unable to give the mortality of cases since discharge from hospital.

(ii) *On re-examination.* The present series consists of cases which were admitted to this hospital with acute nephritis between the years of 1927 and 1938, and the patients were therefore seen one to twelve years after the acute attack. No cases seen for the first time in the latent stage, or in exacerbations, or in the degenerative stage, are included in the series. The re-examination consisted of questioning about general health and further upper respiratory infections since the acute nephritis; determination of weight, height, blood-urea, blood-pressure, and an examination of the urine, which included a quantitative estimation of albumin and microscopy of centrifuged deposit.

The determination of blood-pressure in children calls for especial care. It will be noted that many of our cases when seen at the re-examination were over 12 years of age, but others were still small children when they attended for re-examination. Every care, therefore, had to be taken to eliminate the emotional factors. After a brief talk with the child the armlet was applied, the band inflated, but no reading taken, and the child was thus able to discover the painlessness of the test. The mother was then questioned as above. A blood-pressure estimation was made, the child weighed, and then a further estimation was made, and the lowest of the estimations taken for the first reading. One week later the blood-pressure was recorded again and the average of the two readings in the two weeks was used in our series. All readings were taken by one of us, R. S. I., with a mercury sphygmomanometer having an 8 cm. cuff, and with the child in a sitting position. The instrument was checked against another of the same make, and in cases in which high readings were obtained, readings were frequently checked by other residents in the hospital and were found to tally in every case. Our figures for normality and abnormality of the blood-pressure are based on those of Faber and James (1921). Figures for the blood-pressure which were more than twice and less than three times the standard deviation we have taken as 'doubtful', and figures more than three times the standard deviation as 'abnormal'. It might be considered that figures which are twice the standard deviation could be taken as abnormal, but owing to the difficulty of accurate determinations in childhood because of the emotional element, we have preferred to take the high figure of three times the standard deviation as our criterion of abnormality.

The test used for albumin was a nephelometric one, using 3 per cent. salicylsulphonic acid (King and Hazlewood, 1936). The centrifuged deposit was examined for red blood-cells and casts. Red cells averaging more than one per 1/6 field were considered to be of pathological significance. In no

case was there a urinary tract or vaginal infection, or pyrexial illness at the time of re-examination. Two or more specimens were examined in this way at the re-examination in successive weeks. We have classified the results of the re-examination into three groups:—

A. *Active or latent.*

- (i) Cases showing one or more of the following:—

Abnormal blood-pressure.

Excess of red blood-cells in the urine.

Albumin persistently more than 10 mg. per 100 c.c.

- (ii) Cases otherwise falling into Group B, but showing definite puffiness of the eyelids (two cases).

B. *Uncertain.*

Blood-pressure 'doubtful' (twice to three times the standard deviation), with or without a trace of albumin (less than 10 mg. per 100 c.c.).

C. *Probably healed.*

Investigations negative, or albumin less than 10 mg. per 100 c.c. in the absence of other findings.

Table XII is an analysis of the findings on re-examination of the 62 cases which we have classed 'latent or active'.

It will be seen from Tables XII, XIII, and XIV that we have not found the prognosis of acute nephritis to be nearly so good as many other writers have suggested. Of the total number of patients who replied to our letter asking them to attend for re-examination, two-thirds are in the 'active or latent' stage. One other was in the terminal stage with nitrogen retention. We know, in addition, that four have died from uraemia. It is not possible to say how many have recovered, because 11 cases fall into the doubtful class. In any case, two examinations of the urine are insufficient, and we feel that repeated examinations should be made before a patient is considered finally healed.

Table XII and Table XV show the high incidence of hypertension, often of considerable degree, in the patients when re-examined. Seven patients in Group I, one patient in Group II, and two patients in Group III, had systolic blood-pressure of over 150 mm., and in most of these cases there was a corresponding elevation of diastolic pressure. One patient in Group II, six years and nine months after the acute nephritis, had a blood-pressure of 195/100, with 10 mg. per 100 c.c. of albumin, and complained of severe headaches; the blood-urea was 19 mg. per 100 c.c. Nineteen patients had a systolic pressure of more than 140 mm. of Hg. Table XV shows that the longer the duration of the latent stage the more tendency is there for the blood-pressure to be abnormal. Only one case had an abnormal blood-pressure less than two years after the onset, as compared with 10 out of 12 cases when examined more than eight years after the onset of the disease. In practically every case the highest blood-pressure readings were in those who had had the acute nephritis more than six years previously. Eight out of the 10 cases

TABLE XII

*Analysis of Findings on Re-examination in Cases Classed Active or Latent*

	Blood-pressure abnormal.	Blood-pressure doubtful.	Blood-pressure not taken.	Albumin + (more than 10 mg. %).	Albumin + (less than 10 mg. %).	Red cells +	Raised blood-urea.	Puffy eyelids.	No. of cases.
	+	-	-	+	-	-	-	-	11
	+	-	+	+	-	+	-	-	9
	+	-	-	+	-	-	-	-	8
	+	-	-	-	-	-	-	-	8
	+	-	-	-	+	-	-	-	7
	-	-	-	-	-	+	-	-	4
	-	+	-	+	+	-	-	-	3
	-	-	-	-	-	+	-	+	2
	-	-	-	-	+	+	-	-	2
	+	-	-	-	+	+	-	-	2
	+	-	-	-	-	-	-	+	1
	-	+	-	-	-	-	-	+	1
	-	-	-	+	-	-	+	+	1
	-	+	-	+	-	-	-	-	1
	-	+	-	+	-	+	-	-	1
Total	40	5	9	33	13	17	1	5	62

\* Albumin more than 10 mg. per 100 c.c. in every specimen, on three or more occasions.

TABLE XIII

*Relation of Present Condition of Patient to Time Interval Between Onset of Disease and Re-examination*

Group.	Classification.	Time interval between onset of disease and re-examination.				Total.
		1 to 2 years.	2 to 4 years.	4 to 8 years.	Over 8 years.	
I	A. (Latent)	1	10	15	4	30
	B. (Uncertain)	2	—	5	—	7
	C. (Apparently healed)	—	—	2	—	2
	Total	3	10	22	4	39
II	A.	2	2	13	2	19
	B.	1	—	2	—	3
	C.	2	1	6	1	10
	Total	5	3	21	3	32
III	A.	1	3	5	4	13
	B.	1	—	—	—	1
	C.	—	1	3	—	4
	Total	2	4	8	4	18

TABLE XIV

*Summary, Showing Condition on Re-examination*

	Group I.	Group II.	Group III.	Total.
Total A	30	19	13	62
B	7	3	1	11
C	2	10	4	16
Total				89

who had a systolic pressure of over 150 mm. had had the acute attack more than seven years previously.

Table XII shows the relation of the blood-pressure to the urinary findings. It will be seen that 31 of the patients with raised blood-pressure had albumin or red-blood cells in the urine, while in nine cases the urine was clear.

TABLE XV

*Relationship of Present Systolic Blood-pressure at Re-examination to Time Interval Between Onset of the Disease and Re-examination*

Group.	Classification of blood-pressure.	Time interval.				Total.
		1 to 2 years.	2 to 4 years.	4 to 8 years.	Over 8 years.	
I	Abnormal	—	3	11	4	18
	Doubtful	2	1	6	—	9
	Normal	—	3	5	—	8
	Total cases	2	7	22	4	35
II	Abnormal	—	1	8	2	11
	Doubtful	1	—	5	—	6
	Normal	2	3	7	1	13
	Total cases	3	4	20	3	30
III	Abnormal	1	1	5	4	11
	Doubtful	1	—	—	1	2
	Normal	—	1	3	—	4
	Total cases	2	2	8	5	17
Total with abnormal blood-pressure		1 (14.3%)	5 (38%)	24 (48%)	10 (83.3%)	

TABLE XVI

*Summary of Condition of Systolic Blood-pressure on Re-examination*

Classification of blood-pressure.	Group I.	Group II.	Group III.	Total.
Abnormal	18	11	11	40
Doubtful	9	6	2	17
Normal	8	13	4	25

Hypertension has had scanty notice in the literature of latent nephritis (but see Schroeder and Steele, 1939). Osman (1925), described hypertension in the absence of urinary abnormality in five of the 20 cases which he followed up for periods varying from one and a half to twenty-two years. He suggested that it was a transition stage between acute and chronic nephritis, and stated that the same sequence had been noted in cases of war nephritis. Smellie (1926) in a follow up of 16 cases of nephritis for more than ten years, found cardiac hypertrophy and hypertension without urinary abnormality in six cases, and hypertension in several other cases with abnormal urine. Snoke (1937) mentions a rising blood-pressure as a serious sign in the latent stage. Paterson and Wyllie (1926), though not mentioning the question of hypertension in their cases, quote the figures obtained on re-examination of their series. At least six of their 49 cases had hypertension, two of these with

evidence of cardiac hypertrophy. Eight others had evidence of cardiac hypertrophy without hypertension. Their cases were seen less than five and a half years after the onset of the nephritis. It has already been mentioned that Wessler (1914), examining the hearts of latent nephritics by radiological methods, found cardiac hypertrophy in all the eight cases investigated. It must be pointed out, however, that Alvarez (1923) found abnormal blood-pressures in a considerable proportion of boys aged 14 to 16 in a San Francisco High School, none of which had any history of preceding nephritis. Other papers we have studied (Judson and Nicholson, 1914; Faber and James, 1921; Gordon, 1911) do not mention such marked and common variations from the normal as does Alvarez.

An attempt was made to determine whether any other features in the acute stage had any bearing on the eventual outcome. The degree of nitrogen retention in the acute stage was of no significance in this connexion. Twenty-five per cent. of the cases healed and 25 per cent. of the cases latent had a blood-urea of over 50 mg. per 100 c.c. in the acute stage. The removal of tonsils in or after the acute stage, or the recurrence of infection in ear, nose, and throat, seemed to have no bearing on the findings on re-examination. It is difficult to estimate the importance of the age of onset in assessing prognosis in such a small series, but it does seem that the prognosis tends to become worse with increasing age.

It seems likely that the occurrence of an acute exacerbation of the nephritis more than a year after the onset is of serious significance. It is merely a sign of continued activity, but Snoke (1937) pointed out that only 3 per cent. of cases which remained in the latent stage for more than two years subsequently healed, a fact which indicates the serious prognosis given by our series of 89 cases. The figures show that there is no difference in the eventual outcome of the two types of nephritis. Acute 'focal' nephritis has a prognosis no different from that of acute 'diffuse' nephritis. It seems, in fact, that this last criterion for the distinction of the two types is as valueless as the others.

*Further notes concerning the diagnosis of focal nephritis.* We have taken one criterion, the presence or absence of oedema, in the differential diagnosis of the two types of nephritis, and having applied this criterion to all the cases of acute nephritis in the series, have studied the aetiology, symptomatology, mode of onset, degree of nitrogen retention, urinary output, the blood-pressure, and prognosis of all cases classed by this criterion as focal or diffuse nephritis. It may be said that the presence or absence of oedema in itself is not a good distinguishing feature in the two types of nephritis. We have accordingly applied further criteria to our cases of acute nephritis in order to try to distinguish the two types of the disease. It is agreed that focal nephritis is characterized by its freedom from symptoms. It will therefore be useful to study briefly those cases of acute nephritis in which there was no oedema and an absence of symptoms other than haematuria, malaise, and anorexia. A blood-urea estimation was performed in 35 of these cases before the fortieth day of the disease; it was abnormal in 20 (57 per cent.) and normal in 15 (43



per cent.). The blood-urea was above 50 mg. per 100 c.c. in 15 (43 per cent.) of the cases and above 100 mg. per 100 c.c. in two cases. Oliguria was noted in two cases, and in seven the systolic blood-pressure was over 120 mm. of Hg.

We have re-examined 11 of these 46 cases, with the following results.

Years after onset.		Blood-pressure.	Present age.	Urine reports (2 specimens)	Blood-urea.	Remarks.
yrs.	mos.					
6	8	110/80	9	Albumin 40 mg. % No deposit	144	Polyuria
10	8	155/100	16	Urine clear	27	Severe headaches and epistaxes
5	11	132/85	9	Albumin + Red cells +	29	Headaches
4	5	160/100	16	Albumin 50 mg. % Red cells few	23	—
4	6	122/90	7	Albumin 20 mg. % (3 specimens)	21	—
6	5	126/75	9	Albumin trace in 1 specimen	21	—
4	9	115/80	10	Red cells few	16	Headaches
5	7	Not taken	8	Clear	23	—
5	6	126/80	13	Clear	27	—
2	1	122/88	9	Albumin +	21	—
2	1	136/85	5½	Albumin trace in 1 specimen	24	—

It is seen, therefore, that symptomless cases of haematuria without oedema usually exhibit nitrogen retention, may have oliguria and hypertension, and have not a good prognosis. They do not fulfil the other criteria given for the diagnosis of focal nephritis. Having shown that all the criteria for the diagnosis of the condition are of no value, we suggest that acute focal glomerulonephritis is not a clinical entity.

#### *Discussion.*

No advantage is to be gained by classifying diseases unless such differences in signs, symptoms, treatment, and prognosis can be found in groups of cases that it is of value to separate some groups from others.

A fairly extensive review of acute nephritis has not revealed such differences. By a process of elimination it was found that acute focal nephritis cannot be diagnosed clinically. The various criteria accepted as features distinguishing focal from diffuse nephritis were applied to the entire series of cases seen in the hospital. Cases with oedema were found to present precisely the same features as those without. Cases which were symptomless and free from oedema showed nitrogen retention and hypertension, and had not a good prognosis. There is one further argument against the existence of focal nephritis as a clinical entity. It is the occurrence of the cases (mentioned at the beginning of the paper) which are seen in the late stages of the disease with no history of a preceding acute attack. This unknown acute attack must have been so mild that it was unrecognized. The occurrence of oedema would have been noticed, and symptoms must have been slight, so that the picture must have been that of a focal nephritis. But these cases have



passed on to the late stages of the disease, and therefore have a grave prognosis for the future, not the uniformly good prognosis commonly ascribed to focal nephritis. We feel, therefore, that acute focal nephritis is not a clinical entity. We feel that clinically, apart from the special forms mentioned (pyelonephritis, &c.), there is *one* acute nephritis, and that no advantage is to be gained by further classification.

There are certain aetiological factors of which we would like to have more knowledge; for example, the explanation of an epidemic such as that described by Steiner and Johannessen (1906) in which 70 per cent. of the cases of scarlet fever developed acute nephritis. We would like to know what particular factor operates in a chronic or recurrent infection to cause a sudden acute nephritis. Sixty-nine per cent. of our cases are known to have had previous recurrent infections of ear and throat before the onset of nephritis. One child had a chronic empyema for nearly a year before the supervention, without any exacerbation or additional infection, of an acute nephritis which proved fatal. It is difficult to understand why the kidneys of these patients escaped so long. Some say that nephritis is a sudden reply of the kidney to repeated insults. This cannot apply to cases seen in the earliest infancy, or to cases with no known previous infection. It appears that otitis media is especially commonly associated with nephritis. Ninety-eight of our cases either before or during the attack suffered from an acute infection of the middle ear. These are some of the aetiological factors which are difficult to understand.

We should like to be able to present those signs and symptoms in a case of acute nephritis which might serve as indications of the eventual outcome of the disease, but have been unable to do this. We know only that an immediate grave prognosis can be given on a case exhibiting, after the first week, a rising blood-urea, a rising blood-pressure, an increasing amount of albumin in the urine, a decreasing urinary output, the occurrence of convulsions or coma, or the presence of such complications as bronchopneumonia or gastro-enteritis.

As for the ultimate prognosis, the degree of nitrogen retention, the age of the patient, the removal of a septic focus, the nature of the precipitating infection—all seem to have no effect. It is possible that the outcome depends on the particular strain of streptococcus which caused the original infection. It is possible that the outcome in one locality is different from that in another, because one particular strain of organism is endemic in one locality and not in another.

We are unable to tell which particular cases seen in the acute stage are liable to suffer exacerbations, but the occurrence of an exacerbation a year or two after the acute attack is of serious moment. It is an indication of latent activity, and the paper by Snoke (1937)—a paper which all students of nephritis should read—mentions the very grave prognosis which can be attached to cases remaining in the latent stage for two years or more. We should like to emphasize strongly the fact that patients in the latent stage

are well and symptomless. They are able to take part in full work, to play games, and to live normally. Bell (1938) and others have shown how they may remain in this stage for very many years until, often with dramatic suddenness, the kidneys fail. Bell described cases which remained in the latent stage for ten to thirty years, completely free from symptoms, until suddenly uraemia developed and proved fatal, within a few days of its onset. The progress of these latent cases can be studied accurately by the sediment count. The less accurate method of ordinary microscopy of centrifuged deposit may give an indication of the deterioration of the renal condition. The determination of the blood-pressure is a valuable test, and we feel that a grave significance must be attached to a slowly rising blood-pressure in a patient in the latent stage.

Many have stated that cases in which the onset is insidious, cases in which there is no known causative infection, have a worse prognosis than others. We think that many of these cases are probably not acute cases at all, but exacerbations of a latent active process. Parsons (1926) suggested that mild cases may well be confused with exacerbations of previously existing nephritis, and some of our figures tend to support this view. In hardly any of our cases in which an exacerbation followed some months after the acute attack was there an *acute* infectious process which could be said to have caused the exacerbation. The exacerbation occurred quite unexpectedly and suddenly, for no apparent reason. Volhard mentions this phenomenon, and it may well explain how an exacerbation of a latent nephritis, in which there was no known previous acute attack, may exactly simulate an acute nephritis with no known causative infection. If this suggestion be true, it can well be understood how it comes about that such cases have a worse prognosis than cases of true acute nephritis with an acute precipitating infection.

The initial severity of the blow which the kidney receives has already been mentioned. We have suggested that further investigation will show that the maximum nitrogen retention, the maximum degree of hypertension, and the highest degree of oliguria will be found to occur not days but hours after the onset of the disease, at least in many cases, and that improvement is rapid. The explanation may well lie in an acute oedema of the renal tissues which quickly subsides in almost all those who are not going to succumb.

It appears that in the latent stage there is often the gradual development of hypertension. The significance of hypertension in the absence of urinary signs is difficult to assess. It may or may not represent an active process of the kidney lesion, but continued examination of the urine would decide. Nevertheless, hypertension, or albuminuria, however slight, whether orthostatic or otherwise, in a patient known to have had nephritis in the past, must be regarded with very grave suspicion, with a fear of continued activity until observation over a period of many years has shown that the condition is not progressing. The tendency has been to regard the kidney as innocent after acute nephritis unless proved guilty, but we feel that the kidney should be regarded as guilty until proved innocent.

*Summary*

We have presented a study of 301 cases of nephritis in children seen in the acute stage, and of 64 cases seen in subsequent stages.

We have attempted to show that the classification of nephritis has become unnecessarily complicated and have tried to fit all the various classifications into one simple scheme, that given by Addis (1925).

We set out to decide whether anything was to be gained by distinguishing the focal from the diffuse type of nephritis, using the criteria for the diagnosis given by Volhard and Fahr (1914). As oedema is usually accepted as the chief distinguishing feature in the acute stage the cases were divided into three groups:

- I. No oedema.
- II. No oedema other than puffiness of the eyelids.
- III. Definite oedema.

It was found that:

1. No difference between the three groups could be found to lie in the aetiological factors, age and sex incidence, or causative infection.

2. In symptomatology there was no appreciable difference between the groups. There was an almost equally high incidence of such symptoms as vomiting, abdominal pain, and frequency. A high percentage of cases in all groups were symptomless.

3. It was found to be impossible in the majority of cases to estimate the time interval between infection and nephritis, but in those few in which it was possible it was shown that there was no difference in the three groups. The oedematous cases commence at the height of the infection quite as frequently as the non-oedematous.

4. There appears to be no difference in the frequency with which nitrogen retention occurs in any of the three groups. The transient nature of the rise in blood-urea in the majority of cases is emphasized.

5. Hypertension and oliguria in the acute stage were discussed. It was suggested that they were not of value in distinguishing the two types of nephritis.

6. A criterion suggested by some, namely the occurrence of exacerbation of the nephritis as the result of tonsillectomy, was shown to be of no value.

7. It was found that the prognosis in the three groups was equally serious, the majority being in the latent stage when re-examined from one to twelve years after the acute attack. Emphasis was laid on the high incidence of hypertension in the latent stage, in some cases in the absence of urinary abnormality. Our figures showed that the incidence of this hypertension increased markedly with the duration of the disease.

8. Having shown that the presence or absence of oedema is a useless criterion for the distinction of the two types, we applied other criteria used for the diagnosis of focal nephritis and found that they were similarly useless

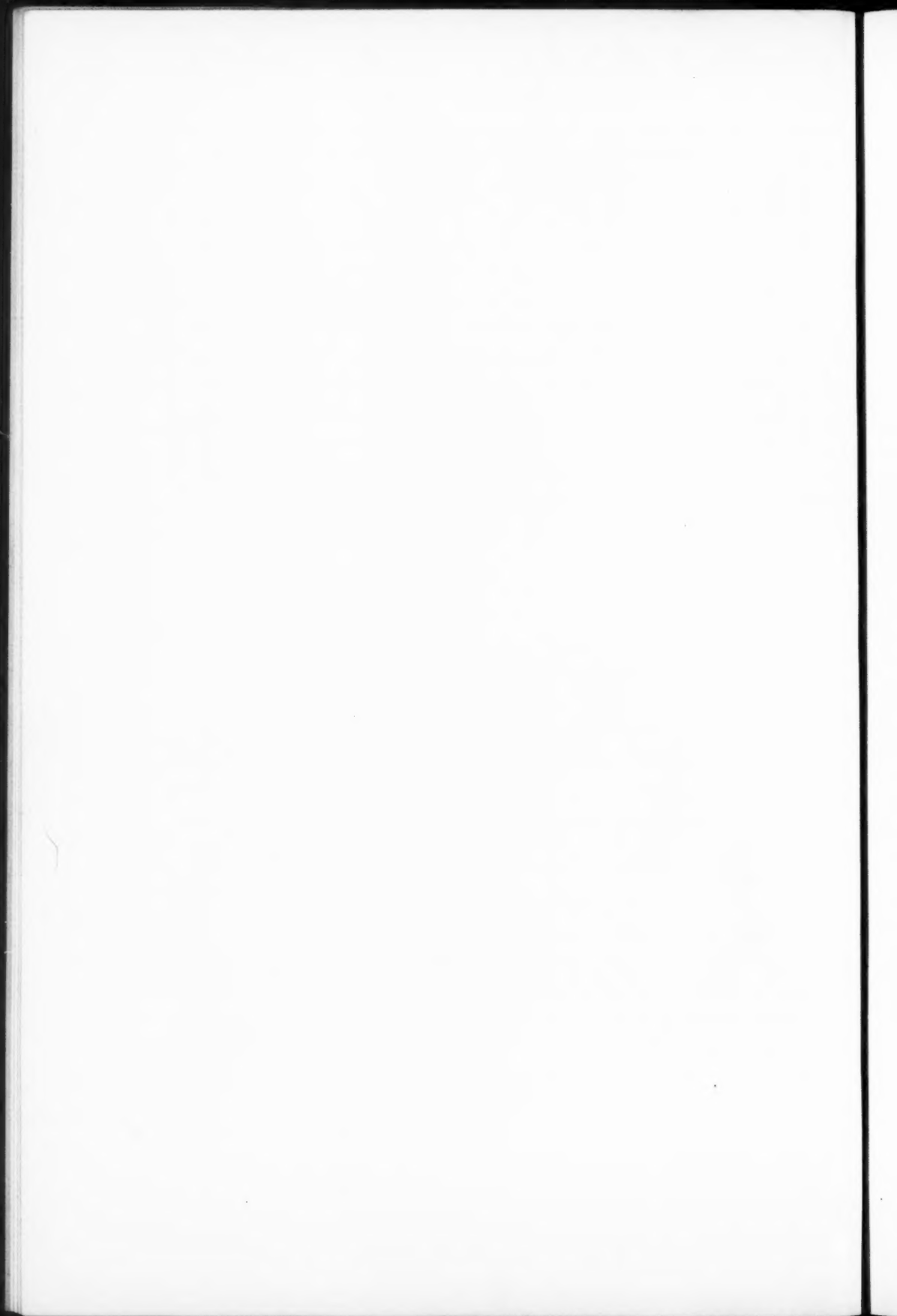
for distinguishing the two types of the disease. We therefore came to the conclusion that acute focal nephritis is not a clinical entity.

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ATYPICAL MANIFESTATIONS OF LEUKAEMIA<sup>1</sup>

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With Plate 4

*Introduction*

THERE is no organ or tissue in the body which has not been involved by leukaemic infiltration, with or without the production of clinical signs and symptoms. Every year many cases are reported in the literature, with unusual symptoms and pathological lesions. Such findings occur as a rule late in the disease after the diagnosis has been firmly established. Their interest, therefore, is greater for the pathologist than the clinician, and they have no important bearing on the fatal course of the disease. In this paper it is proposed to deal only with cases in which the symptoms and the physical signs presented on the first examination were grossly atypical of any of the recognized forms of leukaemia.

Such different disorders as acute thyroiditis, osteomyelitis, tuberculosis, pelvic tumour, subacute bacterial endocarditis, infection of the eye, breast tumour, gall-bladder disease, coronary thrombosis, paroxysmal tachycardia, and brucellosis were considered when the cases to be described were first observed, because the clinical pictures were so suggestive of these diseases. In many instances neither lymphadenopathy nor splenomegaly was present or sufficiently pronounced to attract serious consideration. Furthermore, in the majority the total leucocyte count was not increased, and the first observation to suggest a blood disorder was an unexpectedly severe anaemia. Only after detailed study, and in some instances not until some time had elapsed, was the true nature of the underlying disease discovered.

The 15 cases which are described in this report have been selected because they illustrate the difficulties which may be encountered in the recognition of leukaemia. Only those with satisfactory post-mortem examinations are included, with the exception of one case which was discharged before death. In this case, however, the diagnosis was quite clear by the time the patient left the hospital.

The cases have been arranged in four groups according to the character of the chief presenting symptoms, namely:

- (1) those which suggested some acute inflammatory condition;
- (2) those suggesting abdominal or cardiac disease;

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- (3) those with initial symptoms referable to bones and joints ;
- (4) those characterized by skin changes.

This division is not strictly accurate, because in some instances, as will be observed, more than one of these groups was suggested by the presenting complaints.

Cases of a similar character which have been reported by others are briefly reviewed under each of the above headings. In addition, cases of leukaemia with symptoms referable to other systems, of which we have encountered no well-marked examples, are also reviewed. These additional headings are as follows :

- (5) initial symptoms suggesting disease of the nervous system ;
- (6) initial symptoms directing attention to the chest ;
- (7) initial symptoms referable to the genito-urinary organs.

*Group I. Initial Symptoms Suggesting an Acute Inflammatory Process. (Acute thyroiditis, tuberculosis, osteomyelitis, brucellosis, subacute bacterial endocarditis, conjunctivitis.)*

*Case 1.* Sudden onset of pain ; tenderness and swelling of one lobe of the thyroid ; lack of general lymph-node enlargement or splenomegaly ; relatively acellular marrow on sternal puncture. *Diagnosis* : 'Aleukaemic' myeloid leukaemia.

M. O'N. (127681), an unmarried white woman of 45 years, was admitted on 18.12.37, complaining of weakness, and soreness and swelling in the neck. Symptoms began one month before, after a severe head cold. Six days before admission a sore spot developed in the left lower region of the neck anteriorly. Poor appetite, palpitation, occasional dysphagia, and some fever ensued.

*Physical examination.* Skin : there was marked pallor and a few old ecchymoses, but no petechiae were discovered. Eyes : the sclerae were subicteric ; a tiny, fresh haemorrhage was observed along one artery in the right fundus. Mouth : there was slight redness around the left anterior pillar of the fauces ; the tonsils were small and pale. Neck : the thyroid was easily felt ; the right lobe and isthmus were normal, the left lobe was twice its normal size, smooth, firm, and very tender, but there was little or no local heat. Lymph nodes : there was no general enlargement. The spleen was not felt ; the edge of the liver was at the costal margin. Kidneys : the right was easily felt and was possibly enlarged. Bones and joints : there was tenderness in the lower portion of the sternum.

*Radiology.* Negative.

*Blood.* R.B.C. 1,730,000 per c.mm. ; Hb. 5.4 gm. per 100 c.c. (in all the cases the Newcomer haemoglobinometer, restandardized by the Van Slyke method, was used) ; W.B.C. 5,850 per c.mm. ; myeloblasts 3 per cent. ; undifferentiated myelocytes 13 per cent. ; differentiated myelocytes 8 per cent. ; well-marked polychromatophilia, and two normoblasts per 100 leucocytes ; platelets 121,000 per c.mm.

*Puncture of sternal marrow.* The material obtained on two occasions showed very few nucleated cells. Although a moderate shift to the left in the myeloid series was observed, lymphocytosis was also found.

*Course.* Two petechiae appeared on the mucous membranes of the mouth and then a subcutaneous, smooth, hard, tender tumour about 1 cm. in diameter developed over the left mandible. After two blood transfusions, temporary improvement occurred. The tenderness and swelling of the thyroid subsided slowly and the temperature, which had risen daily to 103° or 104° F., returned to normal. Later, the leucocyte count fell to 1,050 per c.mm. The blood-film continued to show 1 to 21 per cent. myeloblasts, 7 to 45 per cent. undifferentiated myelocytes, and 4 to 7 normoblasts per 100 leucocytes. The platelet count decreased to 25,000 per c.mm., and on 31.1.38 numerous purpuric spots appeared. At this time fever (102° F.), swelling of the face, and enlargement of lymph nodes developed. It was not until three days later that the spleen was first felt. Furuncles developed on the neck. The leucocyte count increased above normal for the first time on 2.2.38 and on 14.2.38 it was 36,700 per c.mm. (74 per cent. myeloblasts). The patient died on 17.2.38.

*Autopsy.* Acute myeloid leukaemia with involvement of spleen, bone marrow, tonsils, cervical, mediastinal, and retroperitoneal lymph nodes, choroid, retina, and meninges.

*Comment.* Acute thyroiditis, tuberculosis, and malignancy of the thyroid, either primary or secondary to a kidney tumour, with myelophthisic anaemia, were considered in the diagnosis. The severe anaemia and the presence of immature leucocytes and normoblasts, as well as thrombocytopenia and sternal tenderness, suggested acute aleukaemic myeloid leukaemia with haemorrhage into the thyroid, a diagnosis which was subsequently shown to be correct.

*Case 2.* 'Osteomyelitis' of right mandible; gums red, swollen, and tender; slight enlargement of spleen and lymph nodes, but none of liver. *Diagnosis:* Myeloblastic chloroma (leukaemia).

C. E. F. (U43600), a white male railroad helper of 25 years, was admitted to the surgical service on 1.6.32, for treatment of osteomyelitis of the right mandible. He had had swollen and bleeding gums for two years which had been diagnosed and treated as Vincent's infection. During the past year he had had four lower molars extracted 'for abscesses'. Bleeding, pain, occasional expulsion of fragments of bone, and swelling of the jaw followed. The pain and swelling persisted, and he began to have fever and loss of weight. Six months before admission, in another hospital, he was thought to have chronic osteomyelitis of the inferior maxilla with secondary anaemia and Vincent's infection of the gums. The blood at that time showed 4,800 white cells per c.mm. with 79 per cent. 'lymphocytes'; four nucleated red cells per 100 W.B.C.

*Physical examination.* Skin: there was extreme pallor, and petechiae were present on the neck and trunk. Eyes: haemorrhages with white centres were present in both fundi. Mouth: the gums were red, swollen, grey, and tender; the jaw was ankylosed. Face: the right side of the jaw and chin were oedematous and red; in the right cheek there was a draining sinus with necrotic edges. The lymph nodes were generally small and firm; the drainage nodes in the right side of the neck were larger. The spleen was felt two finger-breadths below the costal margin; the liver edge was not felt. Bones and joints: there was tenderness over the lower sternum.

*Radiology.* Osteomyelitis of the right mandible.

*Course.* Fever (99° to 105° F.). The patient was desperately ill. Transfusions failed to modify the downhill course, and the patient died on 15.6.32, after two weeks in the hospital.

*Blood.* R.B.C. 2,440,000 per c.mm.; Hb. 6.1 gm. per 100 c.c.; W.B.C. 120,000 per c.mm.; myeloblasts 13 per cent.; undifferentiated myelocytes 83 per cent.; normoblasts rare; platelets reduced in number.

*Autopsy.* Myeloblastic leukaemia (chloroma); myeloid infiltrations and necrosis of bones of face on right side: myeloid infiltration of bone marrow, liver, spleen, adrenals, kidneys, lymph nodes, pancreas, vena cava, heart, pleura, peritoneum, pericardium, periosteum of sternum, retroperitoneal connective tissue, and soft tissues of the neck.

*Comment.* It seemed to be established by the pathological studies that the 'osteomyelitis' was not a true inflammation, but rather leukaemic infiltration followed by necrosis.

*Case 3.* Pain and swelling of right jaw; gums normal; slight enlargement of liver, none of spleen or lymph nodes. *Diagnosis:* Acute myeloid leukaemia (subleukaemic until terminal stage).

C. W. (U48003), a white man of 59 years, was admitted on 25.2.33 complaining of pain and swelling of the right jaw. For the past year he had felt some weakness; this had increased recently, and he had become very pale. Three weeks before admission he developed a severe pain in his right jaw beginning, he thought, as a toothache.

*Physical examination.* Skin: there was marked pallor. Eyes: haemorrhages and exudate were present in both fundi. Mouth: the teeth which remained were carious; the gums were normal. Neck: there was a firm, hard, tender swelling (6 × 7 cm.) below the right ramus of the mandible; inside the mouth a necrotic sinus in the cheek discharged thin purulent fluid; below the swelling were large, tender lymph nodes. There was no general lymph-node enlargement. The spleen was not palpable. The liver edge descended two finger-breadths below the costal margin. In the heart and vessels there were signs of aortic incompetence. The bones and joints were normal.

*Radiology.* Localized osteomyelitis of the right jaw.

*Course.* Fever (100° to 104° F.) throughout. A few petechiae appeared on the trunk. The patient was drowsy and dull, and grew progressively weaker; he died on 5.3.33, nine days after admission.

*Blood.* R.B.C. 2,390,000 per c.mm.; Hb. 6.2 gm. per 100 c.c. In nine days the total white-cell count rose from 55,000 per c.mm. on admission to 275,000 per c.mm. on the day of death. The differential count showed myeloblasts 25 per cent.; undifferentiated myelocytes 39 per cent. There were two normoblasts per 100 W.B.C. The platelet count was 128,000 per c.mm.

*Autopsy.* Acute myeloid leukaemia; myeloid infiltration of organs; moderate arterio- and arteriolo-sclerosis; diffuse scarring of myocardium, scarring and retraction of aortic valve; aortic insufficiency. The swelling in the face was found to be a 'necrotic area bounded by myeloid cells infiltrating into living tissue. The necrotic area is a mass of bacteria; there are some in the living tissue but no phagocytosis is seen.'

*Comment.* As in the last case the process is one of leukaemic infiltration and necrosis rather than active inflammation.

*Case 4.* Chills and fever; sore throat and gums; subcutaneous nodules; recurrent abscesses; positive agglutinations for *B. abortus*; prolonged course. *Diagnosis:* Myeloblastic leukaemia (subleukaemic until terminal stage).

M. F. (152352), a white widowed nurse of 49 years, was admitted on 14.9.38 because of sore throat, aching of the teeth and gums with swelling and soreness of the mouth, 'phlebitis' in the legs, chills and fever, and progressive weakness for two months. She had received sulphanilamide for three days with temporary benefit.

*Physical examination.* The skin was loose and very pale, and there were scattered petechiae; in the subcutaneous tissues of both legs there were many firm, tender nodules with reddish-blue discoloration of the overlying skin. The distribution of the nodules suggested the course of the veins. There was one nodule in the neck. The eyes were normal. Mouth: many teeth were missing; the gums were swollen and greyish-red in colour, with small patches of grey exudate; there were numerous petechiae. There was no general lymph-node enlargement. The spleen was possibly just palpable. The liver edge was at the costal margin. There was no tenderness of the bones and joints.

*Blood.* R.B.C. 2,760,000 per c.mm.; Hb. 7.4 gm. per 100 c.c.; W.B.C. 3,200 per c.mm.; myeloblasts and undifferentiated myelocytes (at first thought by some observers to be 'peculiar' lymphocytes) 66 per cent.; polymorphonuclear neutrophils 5 per cent.; eosinophils 1 per cent.; platelets 132,000 per c.mm. No normoblasts.

*Course.* Slow but progressive increase of weakness, with recurring crops of subcutaneous nodules; development of peri-rectal abscess and of swelling, necrosis, and spontaneous rupture of lymph nodes in right inguinal region on two occasions and failure of the wound to heal; continuous, irregular fever (101° to 104° F.) except for a period when sulphanilamide and sulfapyridine were given, and abscesses were found and drained; fleeting arthralgia and swelling of both knee-joints and left wrist. Agglutinations for *B. abortus* were found positive in a dilution of 1/1280 on 28.9.38, 1/320 five days later, and again on 18.10.38. Blood-culture for this organism was found positive on one occasion. The agglutination titre fell to 1/80 in January and became negative in March. Tuberculin test positive 1:1000. The leucocyte count remained below 5,000 per c.mm. for four months, when it began to rise slowly, reaching 80,000 per c.mm. two months later. The predominating cells were of the same type as originally observed. The platelet count fell to 60,000 per c.mm. Biopsy of the skin was interpreted as suggesting erythema nodosum; that of a lymph node suggested tuberculous adenitis. Sternal puncture, however, revealed a striking preponderance of myeloblasts. The spleen became easily palpable, and the anaemia progressed in spite of repeated transfusions. X-ray therapy was without benefit and death occurred on 7.4.39.

*Autopsy.* Myeloblastic leukaemia. Infiltration of liver, spleen, lymph nodes, and marrow, very slight in kidneys and adrenals. Caseous retro-peritoneal, peri-pancreatic, and pelvic lymph nodes. Caseous tubercles in spleen and liver, containing tubercle bacilli. No evidence of miliary tuberculosis.

*Comment.* Very immature myeloid leucocytes were found in the blood from the beginning, but the discovery of agglutinations for *B. abortus* in high titres, the fever, and the abscesses, as well as the peculiar skin eruption,

suggested brucellosis or disseminated tuberculosis with a leukaemoid reaction, as well as many other conditions. It is possible that the patient had had a brucella infection which was lit up by the new disease.

*Case 5.* Weakness; fever; anorexia; vomiting with streaks of blood; slight enlargement of lymph nodes, spleen, and liver; petechiae. *Diagnosis:* Myeloid leukaemia (subleukaemic).

A. J. (U65101), a coloured labourer aged 50 years, was admitted on 27.9.35, complaining of weakness, shortness of breath, anorexia, and vomiting with streaks of blood in the vomitus, for two months before admission.

*Physical examination.* Skin: there were petechiae on the abdomen and legs. Eyes: haemorrhages and exudate were found in both fundi. Mouth: there were petechiae on the pharynx and buccal mucosa. The lymph nodes were easily palpable, but little enlarged. The liver and spleen were slightly enlarged. The bones and joints were negative.

*Radiology.* Long bones, spine, and skull, normal.

*Course.* After several transfusions the fever diminished, the leucocyte count dropped, and there was general clinical improvement. Nevertheless, purpuric phenomena persisted, the blood-films continued to show myelocytes and normoblasts, and severe anaemia persisted. Later the fever returned, the spleen increased in size, death occurred on 17.11.35.

*Blood.* R.B.C. 900,000 per c.mm.; Hb. 3 gm. per 100 c.c.: W.B.C. 27,500 per c.mm., with myeloblasts 1 per cent., undifferentiated myelocytes 2 to 6 per cent.; occasional normoblasts; platelets 144,000 per c.mm. Later, W.B.C. 7,400, and platelets 10,000 per c.mm.

*Autopsy.* Myeloid leukaemia.

*Comment.* Before death the blood picture was thought to be more indicative of an infection than leukaemia; the main points in favour of the latter were the condition of the eye grounds and the severity of the anaemia, as well as a basal metabolic rate of +40 per cent. when the temperature was only 100° F. One diagnosis seriously considered was subacute bacterial endocarditis. This was supported by a loud blowing systolic murmur, as well as the fever and petechiae mentioned above. Blood-cultures, however, were negative. Chemical poisoning, pernicious anaemia, and miliary tuberculosis were other diagnoses considered.

*Case 6.* Infection of left eye; no enlargement of spleen, liver, or lymph nodes. *Diagnosis:* Monocytosis with visceral infiltration.

W. A. F. (U61456), a white carpenter of 41 years, was admitted on 28.3.35, complaining of an infected eye. For two years he had had persistent bleeding after extraction of teeth. Eight months before admission, incision of an 'abscess' below the jaw was followed by such bleeding that transfusion was necessary. One week before admission he noticed a 'stye' on the left upper eyelid. Photophobia, swelling of the lids, and discharge of thin purulent matter followed. In two hospitals the condition was thought to be gonorrhoeal in origin.

*Physical examination.* The skin was pale, dry, and scaly. Eyes: there was great swelling and oedema of the lids of the left eye; the conjunctivae were oedematous; the iris and cornea were not involved. One small retinal haemorrhage was present in the right fundus. Mouth: the teeth were carious. Lymph nodes: there was no general enlargement;



a few small cervical nodes were palpable. The spleen and liver were not palpable. The bones and joints were normal.

*Course.* Biopsy of the left conjunctiva was followed by profuse haemorrhage necessitating transfusion. The report was 'more mononuclear cells than in an inflammatory lesion; numerous mitoses suggest tumour'. There was also severe epistaxis on one occasion. The bleeding, clotting, and clot retraction times were all normal. Smears of eye secretions and urethral discharge failed to show gram-negative intracellular diplococci. Discharged to Out-patient Dept. on 27.5.35 after deep X-ray therapy over the left eyelid had caused a great decrease in its size. Re-admitted on 2.12.35, complaining of nose-bleedings, and pain in the face.

*Physical examination.* The skin was dry and scaly; there were bruises, but no petechiae. Crusted superficial, but infiltrated, skin lesions were present, biopsy of which was reported as 'round cells and mononuclears—probably leucocytic infiltration'. Eyes: the lids were swollen; the conjunctivae were infected; the fundi were only poorly seen and apparently normal. Mouth: there was extensive infection; pus was easily expressed from the gum margins. The left maxillary sinus was tender. The face was swollen. A large lymph node could be felt at the left mandibular angle. The axillary and inguinal nodes were palpable. The spleen was not felt. The liver could be felt three finger-breadths below the costal margin.

*Radiology.* Long bones normal. Spine: depression deformity of the first lumbar vertebra, narrowing of the twelfth thoracic vertebra compatible with blood dyscrasia or old injury of long standing (Plate 4, Figure 3).

*Course.* Fever (101° F.); further severe bleeding after extraction of teeth, extensive necrosis of gums. Smears positive for Vincent's organisms. The patient died on 31.12.35, about nine months after first admission.

*Blood.* R.B.C. varied between 3,200,000 and 4,500,000 per c.mm.; Hb. between 6 and 13 gm. per 100 c.c.; W.B.C. were 9,900 per c.mm. at the first admission, fell slowly to 3,600 three months later, and after another five months were 16,000 per c.mm. before death. Monocytes and 'monoblasts' on admission formed 53 per cent. of the white cells, were never less than 30 per cent., and on the last count amounted to 78 per cent. of the leucocytes. Similar cells were abundant in the material obtained by sternal puncture. Normoblasts were very rare in the blood-films and were moderately numerous in the marrow. Platelets ranged from 60,000 to 116,000 per c.mm.

*Autopsy.* 'Peculiar monocytosis with cell infiltration in conjunctivae, sinuses of lymph nodes, bone marrow, and spleen. Hyperplasia of femoral and vertebral marrow.... Osteomyelitis of left maxilla. Gingivitis....'

*Comment.* Although the pathologists have avoided the term monocytic leukaemia in the anatomical diagnosis, the case seems to be typical of monocytic leukaemia, although less acute than is usually seen. It is interesting to note that the first superficial infiltration occurred not in the skin but in the conjunctiva where it produced an inflammatory reaction.

*Case 7.* Pain and failing vision in left eye; white nodule at edge of cornea; enlargement of lymph nodes and liver, slight enlargement of the spleen. *Diagnosis:* Chronic lymphoid leukaemia (subleukaemic) with lymphoid tumour of left cornea.

M. G. (Med.52941), a coloured woman of 39 years, was admitted on 21.3.25,

complaining of pain and failing vision in the left eye, hoarseness, and swelling of the neck. She said that her right eye had been removed four years ago for the 'same trouble that was now in the left'. Her present symptoms began almost a year before admission with fever and swelling below her jaw on both sides. Her voice became hoarse. At the same time her left eye became painful, with a feeling of grit in the eye, running of tears and discomfort in bright light. She spent six months in another hospital where four X-ray exposures were given, producing some decrease in the size of the swellings. All symptoms have persisted and in addition her vision has begun to fail.

*Physical examination.* The skin was pale; there were ulcers on the legs.

Eyes: the right eye had been excised; in the left there was photophobia, lachrymation, blepharospasm, infection, and ulceration at the corneo-scleral margin. Lymph nodes: there was considerable general enlargement. The spleen was easily palpable, and the liver edge was just below the costal margin. The bones and joints were normal.

*Course.* After radium and X-ray therapy the size of the lymph nodes decreased, and the number of white cells fell; later, relapse took place and the patient succumbed with lobar pneumonia.

*Blood.* R.B.C. 3,270,000 per c.mm.; Hb. 7 gm. per 100 c.c.; W.B.C. rose from 15,000 to 37,000 per c.mm. at death. Lymphocytes varied between 50 and 80 per cent.; before death 99 per cent.

*Lymph-node biopsy.* Reported as typical lymphatic leukaemia.

*From ophthalmological report.* 'In the left eye on the limbus in the lower outer quadrant there is a raised white millet-sized nodule. This suggests an infiltrating new growth on the cornea.' (Plate 4, Figure 1.)

*Autopsy.* Lobar pneumonia of right middle lobe. Chronic lymphatic leukaemia with leukaemic infiltration of liver and kidneys. Lymphoid tumour of left cornea.

*Comment.* In this case the diagnoses considered were Hodgkin's disease, tuberculosis, and leukaemia.

*Discussion on Group I.* A few authors have reported acute osteomyelitis as a complication of acute leukaemia, others have recorded clinical diagnoses of osteomyelitis which post-mortem studies have amended by demonstrating that the supposed bony inflammation was in reality a combination of necrosis and leukaemic infiltration. This is well exemplified by cases 2 and 3 of this series. Ehrlich and Forer (1934) reported a case in which a diagnosis of acute osteomyelitis of the left arm was made in a girl of 11 years by clinical and radiological examinations. Migratory joint pains which responded to salicylates occurred. Until five weeks before death the blood picture was normal, and then the white count rose to 184,000 per c.mm. with 58 per cent. myeloblasts. At autopsy Aschoff nodules were found in the heart muscle, and myeloid infiltrations in the usual sites. The lower left humerus showed leukaemic infiltration with periosteal elevation. It is not unlikely that all cases of so-called osteomyelitis terminating in acute leukaemia would on careful post-mortem examination show a process of leukaemic infiltration with necrosis, rather than true active inflammation. The same error may arise in other tissues than bone, and this is well illustrated by Love (1936)



who published a series of 152 cases of leukaemia with manifestations in the mouth, pharynx, nose, throat, and ear. In many of these, the infiltrative swellings, with or without necrosis, had been diagnosed clinically as 'cellulitis', 'trench mouth', 'peritonsillar abscess', and in one case 'diphtheria'. One of his cases may be quoted. A man of 56 years was admitted with a diagnosis of cellulitis of the nose, and conjunctivitis; for several weeks he had complained of nasal obstruction with profuse discharge. There was some lymph-node enlargement, but neither liver nor spleen was palpable. The white-cell count was 35,000 per c.mm. with 70 per cent. lymphocytes; biopsy of tissue from the nose showed typical lymphatic leukaemia.

Eye involvement in all types of leukaemia is well recognized. Retinitis and retinal haemorrhage are frequently observed, and exophthalmos is a classical sign of chloroma. Involvement of the iris, cornea, and sclera with leukaemic infiltrations has been reported by Weve (1932) and others. It is unusual for symptoms arising from such infiltrations to be the first indication of the disease as occurred in cases 6 and 7. A very unusual case with eye involvement is one described by Forkner (1938) in which the first symptom in a girl with chronic myeloid leukaemia was sudden blindness due to a large retinal haemorrhage.

*Group II. Initial Symptoms Suggesting Abdominal or Cardiac Disease.* (Gall-bladder disease, coronary disease, paroxysmal tachycardia, abdominal tumour.)

*Case 8.* Pain in upper abdomen and under sternum; petechiae; no enlargement of spleen, liver, or lymph nodes; tenderness of sternum and ribs. *Diagnosis:* Myeloid chloroma.

W. D. P. (U39297), a white man of 52 years, was admitted on 26.9.31, complaining of pain in the abdomen and under the sternum for two weeks; at first intermittent, crampy, epigastric pains; after some days a gradually increasing substernal pain relieved only by morphine. Diagnosed as gall-bladder disease at another hospital; gall-bladder drained five days before admission. One day before admission sudden severe substernal pain not affected by morphine.

*Physical examination.* The skin was pale and sallow; there were petechiae in the axillae, on the thighs and legs; urticaria was present on the fore-arms and legs. Eyes: no haemorrhages or exudate were observed in the fundi. The lymph nodes, spleen, and liver were not enlarged. There was marked tenderness of the sternum and ribs.

*Course.* Irregular fever; increase in malaise; sudden severe abdominal pain with rigidity, followed by blood in the stools and increase in the purpura. Another similar attack of pain was followed by coma. Death occurred on 15.10.31.

*Blood.* R.B.C. 2,710,000 per c.mm. Platelets 230,000 per c.mm., although in the blood-films they appeared to be reduced in number. W.B.C. varied between 6,000 and 16,000 per c.mm.; myeloblasts up to 7 per cent., myelocytes up to 43 per cent. About 2 per cent. of the cells were extremely large and appeared to be megakaryocytes. Normoblasts were rare.

*Autopsy.* Myeloid chloroma with extraordinary proliferation of megakaryocytes and widespread infiltration of practically every tissue. Ulceration of intestines.

*Comment.* Among the clinical diagnoses considered were gall-bladder disease, coronary disease, blood dyscrasia, and lymphoblastoma.

*Case 9.* Attacks of tachycardia becoming more severe; precordial discomfort. *Diagnosis:* Acute myeloid leukaemia.

E. C. (127956), a white married woman of 50 years, was admitted on 16.1.38, because of severe attacks of palpitation, the pulse at times beating at 180 per minute. These had been present off and on for 22 years, but in the past two months she had had several very severe attacks. Recently some discomfort which radiated to the left shoulder had developed in the left chest.

*Physical examination.* Skin: there was moderate pallor and a suggestion of cyanosis of the nail-beds and lips. Slight pitting oedema was present over the tibiae. The eyes were normal. There were no haemorrhages or exudates. The mouth was normal. Lymph nodes: two small, shotty nodes were palpable under the left angle of the jaw; the right epitrochlear node was enlarged. The heart was normal. Spleen: the tip was just palpable to one observer. The liver edge was at the costal margin. Bones and joints: there was moderate tenderness over the sternum at the fourth interspace: tenderness over a rib just above the left nipple, and over the mid-portion of the right tibia.

*Blood.* R.B.C. 3,030,000 per c.mm.; Hb. 9.7 gm. per 100 c.c.; W.B.C. 5,700 per c.mm.; myeloblasts and undifferentiated myelocytes 47 per cent.; two normoblasts per 100 W.B.C.; platelets 124,000 per c.mm.

*Bone marrow puncture.* Well marked preponderance of myeloblasts and undifferentiated myelocytes.

*Course.* Examinations failed to reveal definite evidence of heart disease. The basal metabolic rate was +17 per cent. The anaemia became more severe, and the W.B.C. increased to 56,000 per c.mm. Ecchymoses developed and the spleen became readily palpable. The course was progressively downhill and the patient died at her home in May 1938. There was no autopsy.

*Comment.* This patient had been treated for several months for 'heart disease'. Paroxysmal tachycardia and hyperthyroidism were seriously considered in the diagnosis.

*Case 10.* Pain in left knee; tumour in left lower abdomen; no enlargement of spleen, liver, or lymph nodes. *Diagnosis:* Acute lymphoid leukaemia (subleukaemic).

J. C. (U73614), a white girl of 14 years, was admitted to the orthopaedic service, 1.10.36, complaining of pain in the left knee. This had come on rather suddenly ten days before; there was no swelling or tenderness. She had no other symptoms.

*Physical examination.* The skin and mucous membranes, the eyes, and the mouth were normal. There was no enlargement of the lymph nodes, and the spleen and liver were not palpable. The bones and joints were normal. Abdomen: a mass was felt in the left lower quadrant; this was thought possibly to be an ovarian tumour.

*Course.* Pain in left knee region was thought to be due to the abdomino-pelvic mass pressing on the nerve trunks. Laparotomy was performed on 5.10.36, and showed the right ovary to be replaced by a large mass; the appendix and terminal ileum were thickened; the iliac and caecal mesenteric glands were twice normal size, and firm. The left ovary, liver, and spleen appeared normal. Sections of the ovarian mass were reported as round-cell sarcoma. Deep X-ray therapy in the lower abdomen and pelvis was begun. In spite of this the general condition deteriorated, there was incontinence of urine and faeces, and the cervical nodes enlarged. Death occurred on 3.11.37.

*Blood.* Hb, 16.6 gm. per 100 c.c.; W.B.C. on admission, 9,050 per c.mm.; two days after laparotomy, 17,100 per c.mm.; six days after first X-ray exposure, 4,150 per c.mm.; two weeks after X-ray therapy, 2,600 per c.mm.; at this point X-rays were discontinued and on the day of death the count was 9,520 per c.mm. A differential count when leucopenia was most marked showed myeloblasts 2 per cent.; myelocytes 6 per cent.; 'juveniles' 4 per cent.; segmented 0; basophils 1 per cent.; monocytes 3 per cent.; 'lymphocytes' 84 per cent. No peroxidase stain was made.

*Autopsy.* Acute lymphoid leukaemia with marked infiltration of the ovaries, uterus, large and small intestines, stomach, spleen, pancreas, liver, diaphragm, pericardium, lungs, kidneys, bone marrow, dura mater around cauda equina, lymph nodes, and mesentery. History of removal of 'round-cell sarcoma' of right ovary. Pleural effusion right; collapse of right lung.

*Comment.* The diagnosis of sarcoma having been accepted, the leucopenia, and particularly granulocytopenia, was attributed to the radiation. Re-examination of the blood-films by one of us revealed numerous lymphoblasts, cells which had originally been mistaken for mature lymphocytes. The autopsy findings suggest very strongly that the abdominal tumour was a leukaemic infiltration and not a separate neoplasm.

*Discussion on Group II.* Abdominal symptoms have been frequently observed in the course of leukaemia, but they usually arise late in the disease and rarely form part of the presenting picture. In the acute leukaemias, haemorrhage is common, and ulceration as well as secondary inflammation may occur. Diarrhoea may develop and occasionally there may be difficulty in differentiating dysentery and typhoid fever from acute leukaemia (Klostermeyer, 1934). Infiltration in the stomach and intestine have been observed a number of times in chronic lymphoid leukaemia (Boikan, 1931). As a result there may be pain, diarrhoea, symptoms of obstruction, or even peritonitis after perforation. When changes in the blood are absent or slight ('pseudo-leukaemia gastro-intestinalis') real difficulty in differential diagnosis may be encountered, as in the cases described by Biggs and Elliott (1924) and Ikeda (1931).

Infiltrations made up of leukaemic cells are very uncommon in chronic myelogenous leukaemia and have rarely led to diagnostic difficulties. Cheney (1934), however, has reported two cases of this disease in which ascites developed. The leucocytic changes in these cases were slight, and consequently the Banti syndrome was closely simulated. Gittins and Hawksley (1933)

reported a case of acute monocytic leukaemia in an infant of one year in which the main presenting signs were marked abdominal distension and a round mass in each iliac region, later found to be ovarian endotheliomata. Haining, Kimball, and Janes (1935) described a case of monocytic leukaemia in which there was a constricting mass in the rectum causing abdominal distension with pain and absolute constipation. In other cases of monocytic leukaemia in which rectal lesions have been described (Forkner, 1934; Campbell, Henderson, and Croom, 1936), the clinical picture was characteristic of leukaemia, and no difficulty in diagnosis was encountered.

Symptoms and signs of heart failure may develop in leukaemia, chiefly as the result of anaemia. Infiltration in the myocardium is not uncommon, and Costa (1931, 1933) has observed rupture of the left auricle and of the descending aorta as the result of leukaemic infiltration.

### *Group III. Initial Symptoms Referable to Bones and Joints*

*Case 11.* Severe pain in bones; bone tenderness; petechiae; slight enlargement of spleen, liver, and lymph nodes; striking erythroblastosis. *Diagnosis:* Myeloblastic or monocytic leukaemia (subleukaemic).

C. G. (U65205), a white male chemist of 40 years, was admitted to the hospital on 2.10.35, complaining of extreme exhaustion and pain in the bones. This came on about five months before admission and the pain seemed to be 'in the lower ribs themselves'. The pain was severe and not related to breathing. Later he noticed it in his hips, going down into his legs. Later still, he felt the same kind of pain in his skull and at times 'in every bone in his body'. He became gradually weaker, lost weight, and began to get short of breath more easily than normally. He had persistent bleeding after the extraction of two teeth.

*Physical examination.* The skin was pale and sallow; there were numerous petechiae over the abdomen and chest. There were numerous flame-shaped haemorrhages with white centres, in both retinae. Petechiae were present on the cheeks and palate. There was some enlargement of the lymph nodes. The spleen and liver were palpable, but were not greatly enlarged. Bones: there was tenderness over the skull, the lower half of the sternum, and the tips of the eleventh and twelfth ribs. There were no tumours. The joints were normal.

*Lymph-node biopsy.* Myeloid leukaemia.

*Radiology.* On several occasions the bones appeared normal.

*Course.* Fever throughout (100° F.). The joints became slightly swollen, the bone pains grew worse, and the patient became almost blind from retinal haemorrhages. He died in coma on 15.12.35.

*Blood.* R.B.C. 1,000,000 to 2,000,000 per c.mm.; platelets 30,000 to 50,000 per c.mm. W.B.C. 9,400 per c.mm. on admission; 1,200 before death; myeloblasts 3 per cent.; myelocytes 18 per cent.; lymphocytes 15 per cent.; as many as 53 nucleated red cells, including primitive erythroblasts, per 100 W.B.C.

*Bone-marrow puncture of sternum.* Sixty-six per cent. 'myeloblasts', 28 per cent. undifferentiated cells containing nucleoli.

*Autopsy.* Leukaemia; infiltration of bone marrow, lymph nodes, spleen, liver, meninges, testes, and soft tissues about adrenal, pancreas, and kidney. Periosteum of ribs elevated by masses of leukaemic cells.

*Comment.* The bone pains are explained by infiltration below the periosteum. The type of leukaemia in this case has not been settled. The spleen contained obvious myeloid leucocytes such as those seen in extramedullary blood formation. In the lymph nodes, liver, bone marrow, and other tissues another type of cell, non-granular but frequently lobulated, predominated. Reconsideration of this case brings up the possibility that it may have been an unusual instance of monocytic leukaemia rather than myeloblastic.

*Case 12.* Progressive pain and rigidity of the back; pain and effusion in large joints; no enlargement of spleen, liver, or accessible lymph nodes. *Diagnosis:* Myeloid leukaemia (subleukaemic).

M. T. (U39514), a white labourer of 39 years was admitted to the hospital on 7.10.31, complaining of severe pain and rigidity of the back. This began, almost a year before admission, in the lumbar region and gradually radiated to the head and neck.

*Physical examination.* The skin and mucous membranes were pale, but otherwise normal. In the fundi there were haemorrhages bilaterally with small white centres in many; there was swelling of the right disk. The mouth was normal. Lymph nodes: there was no generalized enlargement. The nodes were enlarged and tender only in the angle of the right jaw. The liver and spleen were not palpable. There was tenderness over the lower sternum. No tumours were found. Joints: the spine was perfectly rigid; both shoulders and knees were swollen and red, and there was pain and effusion in the larger joints. Fluid drawn from the knee-joint was thick and yellowish and contained many cells, 95 per cent. of which were polymorphonuclear neutrophils.

*Radiology.* There was marked atrophy of the spine, especially in the thoracic region, but no evidence of the Marie-Strumpfel type of arthritis. The right ankle was completely ankylosed. The femora and humeri were normal. The lungs were clear, except for small fibroid scars at the left apex.

*Course.* Fever throughout (100° F.). A few petechiae developed on the shoulders and knees. Anaemia progressed in spite of transfusion. After increasing weakness, death occurred on 24.11.31.

*Blood.* R.B.C. always about 1,000,000 per c.mm., Hb. 4.0 gm. per 100 c.c.; W.B.C. 8,150 per c.mm. on admission; 10,000 before death; myeloblasts 9 per cent.; undifferentiated myelocytes 31 per cent.; lymphocytes 29 per cent. on admission, later 8 per cent.; platelets 80,000 per c.mm. Normoblasts were rare.

*Autopsy.* Myeloid leukaemia; myeloid infiltration in viscera. Bronchial, mediastinal, mesenteric, and retroperitoneal lymph nodes enlarged. Disseminated tuberculosis.

*Comment.* No reference to vertebral joints in autopsy records. The typical myeloid infiltrations found at autopsy support the diagnosis of true myeloid leukaemia with terminal dissemination of a dormant tuberculosis, rather than one of tuberculosis with a leukaemoid blood picture.

*Case 13.* Pain in the back, preceded by pain and swelling of left ankle; no enlargement of spleen, liver, or lymph nodes. *Diagnosis:* Myeloid chloroma (subleukaemic).

F. T. (U69340), a coloured woman of 59 years was admitted to the hospital on 10.6.36, complaining of weakness and pain in the back, which she said



had been preceded by redness, swelling, and pain in the left ankle. Four months previously she had had an abscess in her right breast, with a small lymph node palpable in the axilla on that side. She also said she was weak and tired, and had had tarry stools and one small haemoptysis.

*Physical examination.* The skin was pale. There was an ecchymosis below the left eye, and many petechiae, especially in the mucous membranes. There was oral sepsis. Haemorrhages with white centres were scattered over both optic fundi. There was no general enlargement of lymph nodes, and the spleen and liver were not palpable. The bones and joints were normal.

*Radiology.* Skeleton showed no changes suggesting leukaemia.

*Course.* Continuous fever (100° to 104° F.); rapid downhill course. Death occurred on 17.6.36.

*Blood.* R.B.C. 1,340,000 per c.mm.; Hb. 4.0 gm. per 100 c.c.; W.B.C. 47,000 per c.mm.; myeloblasts 17 per cent.; undifferentiated myelocytes 18 per cent.; platelets 100,000 per c.mm.; one normoblast per 100 W.B.C.

*Autopsy.* Myeloid chloroma. Tumour nodules in the ribs and sternum. Invasion of marrow of femur, vertebrae, and skull. Involvement of kidneys, spleen, periportal areas of liver, epicardial fat, lungs, abdominal and thoracic lymph nodes, and hypophysis. Leukaemic retinitis and meningitis . . . numerous haemorrhages.

*Comment.* The pain in the back was almost certainly due to the leukaemic infiltration of the vertebrae. Whether the pain and swelling of the ankle, which she said had been present before her admission, were associated with the leukaemia is difficult to determine.

*Discussion on Group III.* That the bones and joints are frequently involved in leukaemia is well recognized, and much has been written on this aspect of the disease. The changes found include bone tenderness, an established and useful diagnostic sign, probably produced by the rapidly increasing marrow eroding the bone; bone tumours, mainly chloroma deposits; destructive and absorptive lesions leading to softening and fractures; 'osteomyelitis', to which reference has already been made; and arthritis, usually recurrent and migratory in character, and often associated with subperiosteal infiltration, although in the few instances where the joints themselves have been examined *post mortem* no significant changes have been found.

Only those cases in which symptoms due to bone lesions were the first to be noticed or were so severe as to dominate the clinical picture, will be mentioned. In some cases the symptoms have been those typical of rheumatic arthritis with redness and effusion. Strauch (1913) was one of the first to emphasize 'articular rheumatism' as the presenting picture of acute lymphatic leukaemia in children. Cases of this type include those described by Hunter (1927), acute myeloblastic leukaemia in a boy of 12 years, and aleukaemic lymphatic leukaemia in a boy of four and a half years; by Sutton and Bosworth (1934) who described a child of three years with symptoms of recurrent and extensive polyarthritis (but without carditis) who developed adenopathy and the typical picture of acute lymphatic



leukaemia only after six months; and by Seward (1930) in which, in a man of 31 years, the affected joints were found to be normal at autopsy, although the typical histological changes of lymphatic leukaemia were found. The last is one of the few cases in which there is any mention of the joints having been examined *post mortem*. In this connexion the case of Conybeare (1936) is particularly interesting. A boy of 8 years developed acute leukaemia which began with a classical picture of Still's disease. Before death the white-cell count was 20,000 per c.mm., with 30 per cent. lymphoblasts and 60 per cent. lymphocytes. Examination *post mortem* confirmed the diagnosis, and in the right knee-joint small haemorrhages were found on both articular surfaces. Other similar cases have been reported by Smith (1933), myeloid leukaemia in a boy of 12 years; Barney (1933), myeloblastic leukaemia in a man of 53 years; and Henschen and Jezler (1935), aleukaemic myelosis in a man of 56 years.

In other cases pain has been felt along the length of the limbs rather than in the joints themselves, and in these cases periosteal infiltration and elevation has been often found at autopsy. Taylor (1926) described such a case in a child of two years and ten months. The chief complaint was swelling and tenderness of the legs and arms, with progressive weakness making walking impossible. The white-cell count rose from 1,900 to 147,000 per c.mm. before death. Autopsy revealed lymphatic leukaemia, with infiltration of the subperiosteal tissues. Karelitz (1927) had a similar case, also in a young child, but this was of the myelogenous type. Here the illness began with swelling of the fingers, followed by swelling and tenderness of the feet and elbows. Fever, and pain in the abdomen and legs, also occurred. Late in the disease the blood-count showed 33,000 leucocytes per c.mm. with 66 per cent. myelocytes, and a diagnosis of acute myelogenous leukaemia was then made. Periosteal elevations were demonstrated radiologically. Poynton and Lightwood (1932) reported a similar case in which the post-mortem examination showed infiltration and elevation of the periosteum of the femora and humeri with lymphocytes. It has long been recognized that in chloroma the clinical picture may be confusing when the blood changes are not marked, and Kandel (1937) has recently reviewed the subject.

#### *Group IV. Presence of Skin Lesions as First Evidence of Leukaemia*

*Case 14.* Reddish-purple colour of face suggesting erythraemia; lumps all over body; marked enlargement of lymph nodes. *Diagnosis:* Lymphoid leukaemia with leukaemia cutis (subleukaemic until terminal stage).

T. McK. (U64675), a white male mechanic of 58 years was admitted on 7.9.35, complaining of change in the colour of his skin and the development of lumps all over his body. For six months he had noticed that he bruised easily and then, first on the face, there had come pink spots turning into purple lumps. He had become weak and had lost weight.

*Physical examination.* Skin: the face looked purple, and felt nodular and indurated (Plate 4, Fig. 2); small nodules were present on the trunk and arms, none on the legs; there were purpuric spots on the

back. Eyes: a small white exudate was found in the right fundus. The nose was obstructed due to adenoid hyperplasia. Mouth: the teeth were carious; the left tonsil was bluish red. Lymph nodes: there was no marked general enlargement. Spleen: the tip was felt. The liver was slightly enlarged. Bones and joints: there was tenderness over the distal end of the left ulna, and the proximal and middle portions of the right tibia.

*Radiology.* In both arms, the left leg and foot, and throughout the vertebrae, there were areas of radiolucency compatible with leukaemia. There was collapse of the body of the ninth thoracic vertebra. Extensive abnormal porosity of the skull. Pelvis normal.

*Course.* Fever ( $99^{\circ}$  to  $102^{\circ}$  F.). Nasal obstruction relieved by radium. Dyspnoea, anaemia, and purpura progressed. Liver and spleen enlarged. Death occurred on 17.12.35.

*Blood.* R.B.C. 4,500,000 per c.mm. on admission, 1,050,000 per c.mm. on day of death. Platelets 102,000, later 60,000 per c.mm. W.B.C. 4,850 per c.mm. on admission, and 171,000 on the day of death. Differential count on admission, lymphoblasts 1 per cent., lymphocytes 44 per cent.; at time of death, lymphoblasts 84 per cent., lymphocytes 6 per cent. Two normoblasts per 100 W.B.C.

*Autopsy.* Lymphoid leukaemia, with leukaemia cutis.

*Comment.* The leukaemic nature of the condition became obvious as the disease progressed.

*Case 15.* Red mark on abdomen; fever; headache; masses in breasts; marked enlargement of liver; slight enlargement of lymph nodes and spleen.

*Diagnosis:* Acute lymphatic leukaemia.

D. R. a white woman of 24 years complained of headache, fever, and a rash on the abdomen.

*Physical examination.* The skin was pale; on the abdomen, a red macular eruption was observed; later copper-coloured nodules 5 to 10 mm. in diameter could be felt in the skin of the abdomen. Eyes: exudate and haemorrhages were present in both fundi. Mouth: the gums were swollen and ulcerated. Breasts: firm, flattened masses about the size of a shilling were felt in both breasts. Lymph nodes: there was slight enlargement. Spleen: the tip was just palpable. Liver: the edge was felt at the umbilicus. The bones and joints were normal; there was no tenderness.

*Course* Irregular fever ( $104^{\circ}$  F.). Progressive stupor. Death occurred on 12.12.36, about three months after the onset.

*Blood.* R.B.C. 1,860,000 per c.mm. W.B.C. varied between 1,100 and 2,400 per c.mm. Lymphoblasts 3 per cent.; lymphocytes 83 per cent. Platelets 78,000 per c.mm. No normoblasts.

*Autopsy.* Acute lymphatic leukaemia with infiltration in breasts, liver, spleen, lungs, skin, pancreas, ovary, adrenals, and bone marrow.

*Comment.* The breast tumours and the blood changes suggested malignancy with bone-marrow metastases, but the skin changes and immature leucocytes favoured leukaemia.

*Discussion on Group IV.* The skin lesions found in leukaemia may be divided into the true leukaemic infiltrations, and the non-specific leukaemids, which include petechiae, vesicles, pustules, wheals, herpes zoster, etc. The

former, leukaemia cutis, is rare in the myelogenous form, but not uncommon in the lymphatic and monocytic types. It is, however, quite exceptional for lesions to appear in the skin as the first or even as an early sign of the disease. Ketron and Gay (1923) reported a case in which bluish-red nodules were spread all over the body. There was enlargement of the liver and spleen,

TABLE I  
*Summary of Clinical Data in 15 Cases*

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Myeloid.	Myeloid.	Myeloid.	Myeloid.	Myeloid.	Monocytic.	Lymphoid.	Myeloid.	Myeloid.	Lymphoid.	Myeloid or monocytic ?	Myeloid.	Myeloid.	Lymphoid.	Lymphoid.
Age	45	25	59	49	50	41	39	52	50	14	40	39	59	58	24
Sex	F	M	M	F	M	M	F	M	F	F	M	M	F	M	F
Lymph nodes	-	±	-	-	±	-	+	-	+	-	±	-	±	++	±
Spleen	-	+	-	±	+	-	+	-	±	-	±	-	-	+	±
Liver	-	-	±	-	±	-	+	-	-	-	±	-	-	±	+
Bones	+	+	-	-	-	-	-	++	+	-	+	+	-	+	-
Purpura	+	+	-	+	++	+	-	++	+	-	++	-	+	+	-
Pallor	++	++	++	++	+	+	+	+	+	-	+	+	+	-	+
Gums	-	+	-	+	-	±	-	-	-	-	-	-	±	+	+
Retinae	+	++	++	-	++	+	0	-	-	0	-	++	++	+	++
Fever	104	105	104	104	104	101	-	101	-	100	100	100	104	102	104
Duration	4	24	52	8	8	104	52	2	8	2	20	52	12	26	7
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	8	2	1	28	7	36	52	2	16	4	6	6	1	3	5
	Inflammations						Abdomen and heart			Bones and joints			Skin		

*Legend:* Comments regarding lymph nodes, spleen, and liver refer to enlargement; those regarding bones refer to tenderness; and those regarding gums refer to swelling.

++ = very marked

Retinae: ++ = haemorrhages in both fundi

+ = present

+ = haemorrhages in right fundus only

± = doubtful or very slight

Duration: 52 = weeks from onset of symptoms to admission

0 = not examined

+

- = negative

6 = weeks from admission to death

but the blood showed only anaemia. After two months the skin nodules disappeared and the liver and spleen decreased in size. One month later, the nodules reappeared, the liver and spleen enlarged, and the blood became typical of myeloid leukaemia. Biopsy and autopsy confirmed the nature of the condition. Boardman (1928) reported a case of lymphatic leukaemia which began with universal exfoliating erythroderma. Arzt (1930), Herxheimer (1925), and others have described skin lesions, thought to be leukaemic, in cases in which the blood showed slight or no changes, but in many instances proof of the leukaemic character of the disease is wanting.

#### *Initial Symptoms Suggesting Involvement of Other Systems*

Although our own records do not include cases in which leukaemia made its first appearance by simulating disease of systems other than those already discussed, such cases as reported by others may be considered briefly here.

TABLE II  
Summary of Initial Blood Findings

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15					
R.B.C.	1.73	2.44	2.39	2.76	0.85	3.25	3.27	2.71	3.03	—	1.92	0.89	1.34	4.50	1.86					
Hb.	5.4	6.0	6.2	7.4	3.0	6.3	7.0	8.0	9.7	16.6	5.5	3.7	4.0	12.8	5.0					
M.C.V.	98	89	83	88	93	78	—	81	96	—	94	103	90	84	82					
Polych.	++	—	+	±	±	±	—	—	+	—	++	—	±	+	—					
N.R.C.	2	—	2	—	4	1	—	±	2	—	53	—	1	2	—					
W.B.C.	5.9	124.0	55.0	3.2	27.3	9.9	15.3	9.3	5.7	9.1	9.5	8.2	47.0	4.9	1.1					
Myeloblasts	3	13	25	—	1	—	—	3	—	2	3	9	17	—	—					
Un. myelocytes	13	83	39	66	6	—	—	5	47	—	—	31	18	—	—					
Diff. myelocytes	8	1	20	—	18	—	—	2	2	6	18	14	21	1	—					
Juveniles	11	—	9	—	40	11	—	10	8	4	22	9	20	14	7					
Segmented	27	1	3	6	29	16	47	65	9	1	38	8	2	27	7					
Lymphoblasts	—	—	—	—	—	—	—	—	—	—	—	—	—	1	3					
Lymphocytes	35	2	3	27	2	20	52	7	34	84	15	29	2	44	83					
Monoblasts	—	—	—	—	—	37	—	—	—	—	—	—	—	—	—					
Monocytes	—	—	1	1	4	16	1	8	—	3	4	—	—	13	—					
Platelets	121	124	128	132	144	60	—	236	124	—	53	124	100	102	78					
B.T.	4	5	1	1	18	4	—	4	8	—	14	—	2	—	—					
Inflammations															Abdomen and heart		Bones and joints		Skin	

Legend: Red-cell count (R.B.C.) is given in millions per c.mm., haemoglobin (Hb.) in gm. per 100 c.c., mean corpuscular volume (M.C.V.) in cubic microns, number of leucocytes (W.B.C.) and platelets in thousands per c.mm., bleeding time (B.T.) in minutes, the different types of leucocytes in per cent. The number of nucleated red cells (N.R.C.) is given as the number per 100 W.B.C. or is indicated as rare (±) or none (—). Under polychromatophilia of the red cells (Polych.) these designations are used, as well as + for slight or moderate, ++ for well-marked. 'Un. myelocytes' refers to early myelocytes (sometimes called 'A' and 'B', or 'premyelocytes') which are undifferentiated as regards the type of granulation, as distinguished from 'Diff. myelocytes' in which the distinction between neutrophilic, eosinophilic, and basophilic forms is clear.

*Group V. Initial Symptoms Suggesting Disease of the Central Nervous System*

In all types of leukaemia histological changes in the nervous system are frequently found, although, according to the study of Schwab and Weiss (1935), neurological signs have been observed in only about 25 per cent. of such cases. Any part of the nervous system or its meninges may be involved, and the lesions may take the form of haemorrhage, thrombosis, infiltration with leukaemic cells, or tumour-like growths. Frequently from the whole clinical picture it is evident that one is dealing with leukaemia, but in some instances the symptoms and signs have directed attention chiefly or even exclusively to the nervous system. Some of these cases may be cited. Munro (1920) described a case of acute myelogenous leukaemia in which the onset was characterized by fever, vomiting, delirium, stiffness of the neck, and positive Kernig's and Babinski's signs. In Blaschy's (1929) patient, the illness began with pain and paralysis of both legs. Signs of polyneuritis of all four limbs developed and the patient was found to have chronic lymphatic leukaemia. Critchley and Greenfield (1930) described three cases of chloroma in which the presenting symptoms and signs were (1) pain in the back, numbness and helplessness of the legs, retention of urine, and exophthalmos; (2) spasms of severe abdominal pain, complete left facial palsy, retention of urine, and later, flaccid paralysis of both legs; (3) weakness and numbness of the legs, difficulty of micturition, and later, left facial paralysis and deafness in the left ear.

In the patient described by Haintz (1933), the first complaint was inability to micturate and incontinence of faeces. Vision and hearing then became impaired. Examination revealed a left facial palsy with anosmia on the same side. Muscular power was diminished on the left side. There was a nodule on the left parietal bone, and another on the seventh rib on this side; the axillary and inguinal lymph nodes were slightly enlarged; neither the liver nor the spleen was palpable; the sternum and vertebral spines were tender. The white-cell count was 26,000 per c.mm. with 56 per cent. myeloblasts and 14 per cent. myelocytes. *Post mortem* green tumours were found in both orbits, another pressing on the left side of the medulla, and there was extensive infiltration about the cord. Garvey and Lawrence (1933) collected three cases of acute lymphatic leukaemia beginning with facial paralysis. In one case this was bilateral and included the taste fibres; in the other two, the right facial nerve only was involved. Although the cervical lymph nodes were enlarged from the onset, the liver and spleen did not become palpable, nor did the blood picture suggest leukaemia until late in the disease. In the one case which came to autopsy, the first, the meninges and both facial nerves were found to be infiltrated with lymphocytes. Schwab and Weiss (1935) had a similar case, in which left facial paralysis was accompanied by difficulty in swallowing. On admission, the white-cell count was 14,000 per c.mm. with only 40 per cent. lymphocytes; later, however, many lymphoblasts appeared. The post-mortem findings were characteristic of lymphatic leukaemia. Diamond (1934) reported 14 cases of leukaemia in which



involvement of the nervous system was found. Pain or paralysis resulting from involvement of cranial and peripheral nerves were presenting complaints in four cases.

*Group VI. Initial Symptoms Directing Attention to the Chest*

Cooke (1932) reported four cases in which tumours in the thymic region preceded the blood picture of acute leukaemia. Mediastinal tumour from lymph-node enlargement may be the chief manifestation of lymphatic leukaemia. That pulmonary disease may be simulated by leukaemia is indicated by the remarkable case of Joachim and Loewe (1927) in which the presenting complaints were productive cough, fever and profuse sweats, loss of weight, rusty or frankly sanguineous sputum, dyspnoea, and occasional chest pain. These symptoms were shown to be embolic and infarctive in origin. Splenic and lymph-node enlargement were absent at first, but there was profound anaemia as well as leucopenia. The case was shown at autopsy to be one of myeloid leukaemia.

*Group VII. Initial Symptoms Directing Attention to the Genito-urinary Organs*

Although infiltration of the kidneys is a common finding in leukaemia, it is unusual for attention to be directed early in leukaemia to the genito-urinary organs except when haemorrhage occurs. Haematuria is not at all uncommon. In one of the patients of Locke and Minot (1924) haematuria appeared before other signs of leukaemia were manifest. In Gwyn's (1930) case of acute leukaemia the onset was marked by acute pain in the renal region and marked haematuria. Priapism has been mentioned frequently as a symptom of leukaemia. Forkner (1938) states that it may be the first manifestation of the disease. Mach (1931) describes a case of myeloblastic leukaemia which was first taken to be acute nephritis because of oedema and the presence of casts, red blood-cells, and leucocytes in the urine. One of us (Wintrobe and Hasenbush, 1939) has observed three patients who first presented themselves because of symptoms of prostatic hypertrophy, and were discovered to have early chronic lymphatic leukaemia. The prostates, removed from two of the patients, showed infiltration with lymphocytes as well as typical prostatic hypertrophy.

*General Discussion*

From the analysis of the appended tables, certain features can be seen to be more consistent than others, and may be of value in arriving at the true diagnosis in spite of a combination of symptoms and signs suggesting other diseases. The cases described include nine instances of myelogenous leukaemia, four of the lymphatic type, one monocytic, and one of undetermined type, possibly myelogenous or monocytic. All the cases except two were febrile. Several can be classed as 'acute' and one as 'chronic', but the majority fit neither of these designations as they are usually understood. The total duration of illness ranged from four to 140 weeks as far as can be



determined from the patients' histories. The average duration was thirty-seven weeks. All but four of the patients died within one to eight weeks of their admission to the hospital. The majority of the cases, therefore, may be described as 'subacute'.

It is noteworthy that enlargement of lymph nodes, spleen, and liver was never a striking feature. Pallor of the skin and mucous membranes was a very prominent sign in most instances, and petechiae occurred in nine, more than half of the cases. Retinal haemorrhages were the most consistently occurring sign. They were found in 10 of the 13 cases examined ophthalmoscopically. Swelling of the gums was not common, this sign having been found in only three myelogenous cases, two lymphoid and one monocytic. In seven cases there was bone tenderness. It may be pointed out that such tenderness was overlooked by a number of physicians who examined these patients, systematic pressure over the bones often being necessary to demonstrate this important sign. In several instances there was a small area of tenderness over the lower portion of the sternum which could be easily overlooked and of which the patient was often unaware.

In seven cases the leucocyte count was normal, in three it was lower than normal, and in five it was increased. In all cases, however, the differential formula was abnormal, although immature leucocytes were found in great numbers in relatively few instances.

The great severity of the anaemia in a number of cases is worthy of comment. In two patients the erythrocyte count on admission was less than one million cells per c.mm. It is customary to think of pernicious anaemia as the classical example of a type of anaemia of such insidious development that it may be advanced to an extreme degree before the patient seeks assistance. Well-marked macrocytic anaemia was found in one case and a moderate average increase in the size of the cells was found in two more. Since leucopenia is found in pernicious anaemia, it is apparent that there may be reason to confuse the blood picture in some instances of 'aleukaemic' leukaemia with that of pernicious anaemia. Nucleated red cells were found in all but four of the 14 cases in which the blood-films were examined with sufficient care. In one case (number 11) they were very numerous. Chiefly normoblasts were observed and none of the very primitive types seen in pernicious anaemia in severe relapse were found. Polychromatophilia of the red corpuscles was also common, and the percentage of reticulocytes was often increased above normal.

In all but one of the 13 cases in which a platelet count was made, there was thrombocytopenia. However, in many instances this was not very marked when the patients were first examined, and bleeding time as well as clot retraction often were not appreciably prolonged. The tourniquet test for capillary resistance was found positive in the few instances in which the test was made. Coagulation time was normal in every case.

The cases described appear to be instances in which a leukaemic process began insidiously and progressed sometimes very slowly, with the main

infiltrations in tissues other than the blood, spleen, liver, and lymph nodes, thus producing an atypical clinical picture. Sooner or later, however, the rate of advance of the disease was greatly, and apparently in most cases suddenly, accelerated with the production of fever, retinal haemorrhage, severe anaemia, and purpura, sometimes enlargement of spleen and lymph nodes, and often leucocytosis just before death. An early diagnosis can be made in these cases only if the possibility of leukaemia is always kept in mind and a complete physical and blood examination is made. Clinical findings which suggest leukaemia include (1) nerve root and deep bone pains, (2) symptoms of arthritis, (3) tumefaction of the gums, (4) even slight enlargement of lymph nodes or spleen, (5) unexplained fever, (6) bone tenderness, (7) unexplained purpura and retinal haemorrhages, and, as Baldridge and Fowler (1933) have pointed out and cases 2, 3, and 15 illustrate, (8) reddish-grey, non-liquefied tissue at operation for osteomyelitis, and (9) unexplained acute enlargement of the breasts and ovaries.

Important laboratory findings include (1) increased basal metabolic rate, (2) high blood uric acid, (3) osteolytic, myelosclerotic, or tumour-like changes in bones examined radiologically, (4) severe unexplained anaemia, (5) nucleated red cells, diffuse and punctate basophilia, and increased reticulocytes in the presence of an otherwise 'aplastic' blood picture, (6) unexplained macrocytic anaemia, (7) leucopenia due to a reduction in all types of cells and yet marked by the presence of a few immature cells. The latter must be deliberately looked for because, as cases 2, 4, and 10 indicate, they may be mistaken for lymphocytes.

Of all the disorders of the blood, aplastic anaemia is the one which is most often confused with aleukaemic leukaemia. Cases of the latter disease which presented a picture resembling aplastic anaemia, have been described by Mettier and Purviance (1937) and by Hickling (1937) as well as others, and we have observed several examples. The onset is insidious, there may be no enlargement of spleen or lymph nodes, and the presence of severe anaemia, leucopenia, and thrombocytopenia suggests aplastic anaemia. Thorough study, however, usually reveals some of the significant findings which have just been enumerated. Hodgkin's disease, myelophthisic anaemia resulting from metastases in bones, and osteosclerotic anaemia must also be distinguished from aleukaemic leukaemia.

In the recognition of aleukaemic leukaemia, examination of the sternal marrow is very helpful. Marrow obtained by puncture of the sternum often contains a large proportion of immature leucocytes which are quite numerous and uniform in type, making the diagnosis clear. It must be pointed out, however, that occasionally such a preponderance of a single cell type is not found, as occurred in case 1, and the sternal puncture may be actually misleading if it is interpreted without due appreciation of the fallibility of the method. Biopsy of sternal marrow is less likely to be misleading, and it is our custom to resort to this when sternal puncture fails to solve the diagnosis.

*Summary*

1. Fifteen cases of leukaemia are described in which, because of an unusual picture on admission, a clinical diagnosis of some other disease was suggested at first, although blood studies and the post-mortem examination proved them to be genuine leukaemia.

2. These cases are considered under the following headings:

- (1) those which suggested some acute inflammatory condition;
- (2) those suggesting abdominal or cardiac disease;
- (3) those with initial symptoms referable to bones and joints; and
- (4) those characterized by skin changes.

3. A number of similar cases from the literature are discussed and additional reported cases are considered as follows:

- (5) initial symptoms suggesting disease of the nervous system;
- (6) initial symptoms directing attention to the chest;
- (7) initial symptoms referable to the genito-urinary organs.

4. The more important features common to our cases are reviewed, and clinical and laboratory findings which are important for the recognition of 'aleukaemic' leukaemia are enumerated.

The authors are indebted to Dr. A. McG. Harvey for notes on a number of the cases and to Drs. H. M. Thomas, Jr. and Warde B. Allan for permission to include cases under their care. This work was done during the tenure by D. M. Mitchell of the Adrian Stokes Memorial Fellowship, Trinity College, Dublin, Eire.

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FIG. 1. Case 7. Lymphoid tumour of cornea, in chronic lymphatic leukaemia



FIG. 2. Case 14. Reddish-purple infiltration of skin of face, especially the cheeks, in lymphatic leukaemia

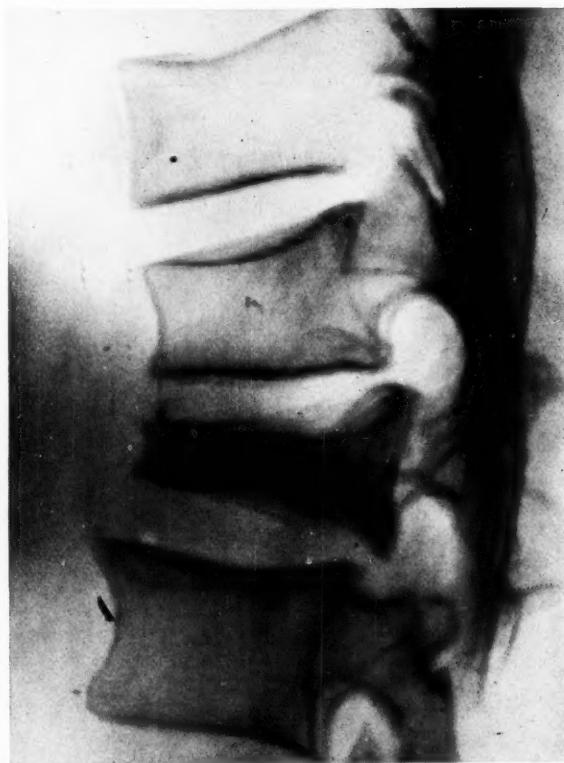


FIG. 3. Case 6. Compression deformity of first lumbar and partial narrowing of twelfth dorsal vertebra, in monocytic leukaemia





THE RENAL CHANGES IN ALKALOSIS<sup>1</sup>

By B. M. NICOL

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Department of Medicine, Edinburgh University)

THE clinical syndrome which occasionally follows the intensive use of alkalis in the treatment of peptic ulcer is now well recognized under the name 'alkalosis'. In this paper 'alkalosis' is used to mean that syndrome; increased alkali reserve of the blood is referred to as 'alkalaemia'. The symptoms are lassitude, depression or irritability, headache, anorexia, and drowsiness. Latent or manifest tetany may be present, and coma may supervene. The patients are often dehydrated, and varying degrees of hypochloraemia, alkalaemia, and azotaemia are found.

Exactly similar clinical and biochemical findings have been described after the vomiting of upper intestinal obstruction (Brown, Eusterman, Hartman, and Rowntree, 1923; Ellis, 1924; Cooke, 1933; Nicol and Lyall, 1939), and it has been shown that the same picture can be produced experimentally by the removal of chloride by continuous gastric aspiration in both animals and man (Dragstedt and Ellis, 1930; McCance, 1938; Bartlett, Bingham, and Pedersen, 1938; Lyall and Nicol, 1939). Renal dysfunction is almost always found in association with these clinical and biochemical disturbances. The relationship between pyloric stenosis and renal changes has been recognized since Nazari in 1896 first described the deposition of calcium in the kidneys of patients dying as a result of this condition. Hardt and Rivers (1923), who first recorded the symptoms of alkalosis accurately, found albumen, casts, and red blood-cells in the urine of patients who were undergoing intensive alkali therapy as part of the treatment of peptic ulcer. Brown, Eusterman, Hartman, and Rowntree (1923) described, in addition to calcification, granular and fatty degeneration of the renal tubular epithelium in cases of alkalosis induced by pyloric stenosis and vomiting, and applied the term 'toxic nephritis' to this change. Cooke (1933) and others have also reported that in this condition the main damage to the kidney is found in the tubules.

The mechanism by which the renal damage is brought about is still uncertain. The structural changes have been variously ascribed to absorption of toxins from the obstructed gut (Haden and Orr, 1923, 1924), to hypochloraemia (Hatano, 1939; Pérez-Castro, 1937), to alkalaemia (Stieglitz, 1924, 1928; Jordan, 1926; Addis, McKay, and McKay, 1926, 1927), and to decreased blood-flow through the kidneys as a result of dehydration (Fishberg, 1939). While Hardt and Rivers (1923) and Berger and Binger

<sup>1</sup> Received August 18, 1939.

(1935) have emphasized that alkalosis from alkali ingestion is apt to occur in patients whose renal function is already impaired, it is clear that pre-existing renal damage does not account for all the cases in this group.

The present investigation concerns the mechanism of the renal disturbance in the alkalosis of pyloric stenosis; it is an attempt to assess the relative importance of alkalaemia, hypochloraemia, and dehydration in its production.

#### *Methods*

Observations were made on two groups of patients: (I) four cases of pyloric stenosis, with severe vomiting, dehydration, and alkalosis; (II) three cases of pyloric stenosis of lesser degree, in which hypochloraemia and alkalaemia were produced experimentally by the restriction of salt intake and withdrawal of gastric contents, over periods varying from two to six days. In two patients of the second group dehydration consequent on removal of sodium chloride from the body was prevented, as far as was possible, by the oral, rectal, and intravenous administration of water or isotonic glucose solution. The third patient was allowed to become dehydrated by restriction of fluid intake during the period of gastric aspiration, but after hypochloraemia and azotaemia had been established the dehydration was corrected by giving water or 5 per cent. glucose solution, while the hypochloraemia and azotaemia were maintained by the continued restriction of salt in the diet.

In all the patients, plasma-chloride and carbon dioxide combining power were estimated in oxalated venous blood collected under paraffin, using Van Slyke's methods; urea was estimated, in the same specimens by the urease method. Degrees of dehydration and anhydraemia were judged from clinical appearances, red blood-cell counts, haematocrit, and haemoglobin readings (haematocrit readings were made after centrifuging the blood for 30 minutes at 3,000 r.p.m.). Urea, chloride, and specific gravity were determined in 24-hour samples of urine, and the reaction of the urine to litmus recorded. Red blood-cells and casts were looked for in centrifuged urine deposits. In the second group of patients, hypochloraemia and alkalaemia were produced in the manner described by Lyall and Nicol (1939). The diet given, consisting of milk and milk puddings, contained slightly less than 2 gm. of chloride (as NaCl) per diem. Through an indwelling Ryle's tube the stomach was emptied at  $\frac{1}{4}$ - to  $\frac{1}{2}$ -hourly intervals during the day and hourly during the night. By this means as much as four litres of gastric contents, containing 30 gm. of chloride (as NaCl) were removed in 24 hours.

The observations make it possible to correlate the urinary evidence of renal damage with changes in blood-urea, plasma-chloride, and carbon dioxide combining power, and with haematocrit values, in the following sets of circumstances:

(a) Hypochloraemia, alkalaemia, and azotaemia, with dehydration (Group I, cases 1, 2, 3, 4).

(b) Hypochloraemia, alkalaemia, and azotaemia, without dehydration (Group II, cases 5 and 6).

(c) Hypochloraemia, alkalaemia, and azotaemia, first with, then without, dehydration, in the same patient (Group II, case 7).

### *Case Reports*

#### *Group I. Patients Admitted in a State of Alkalaemia and Hypochloraemia with Dehydration*

*Case 1.* A man aged 29 years was admitted to hospital complaining of epigastric pain of duodenal ulcer type which had been present on and off for six years. He had vomited frequently during the twelve days before admission. He was drowsy, latent tetany was demonstrable, and he was very dehydrated. Occult blood was present in the faeces and the urine contained albumen, epithelial and granular casts, and a few red cells, and was acid in reaction. He responded well to the intravenous infusion of saline, but vomiting recurred and gastro-enterostomy was performed, after which he made a rapid recovery (Fig. 1).

*Case 2.* A man, aged 47 years, had experienced attacks of epigastric pain for eight years. He had vomited occasionally for one year and daily for fourteen days before admission, and was very dehydrated. He was found to be suffering from alkalosis. His urine contained albumen, epithelial and granular casts, and was acid in reaction. The chemical composition of his blood returned to normal after the administration of saline intravenously, and he made an excellent initial recovery (Fig. 2).

*Case 3.* A woman aged 45 years had complained of epigastric pain for two years, coming on one hour after food. She had vomited occasionally for three months and daily for six days before admission. She was extremely dehydrated, drowsy, and complained of severe headache. The plasma-chlorides were low, and the carbon dioxide combining power and blood-urea were high. She showed latent tetany. Her urine was acid in reaction and contained albumen, and epithelial and granular casts. X-ray examination revealed a large ulcer on the lesser curvature of the stomach. After several days' treatment by gastric lavage and frequent feedings on an intermediate Hurst diet, without alkalis, and the administration of saline by mouth and by rectum, she began to improve and the ulcer healed slowly (Fig. 3).

*Case 4.* A man aged 32 years had suffered from a duodenal ulcer for over two years. He had vomited occasionally for ten months, and daily for six weeks before admission to hospital. He was severely dehydrated and in a condition of hypochloraemia, alkalaemia, and azotaemia. The urine was acid and contained red blood-cells. His blood-pressure was 105/65 mm. of Hg on admission. He was treated by intravenous normal saline infusions, and his condition improved slightly for three days. The dehydration was overcome and the blood-pressure increased to 120/75 mm. of Hg on the fourth day in hospital. The volume of urine passed in twenty-four hours rose from 240 to 960 c.c. The blood-urea, however, continued to rise, the urine diminished in volume, and he died in uraemia ten days after admission (Fig. 4).

*Autopsy report by Dr. A. D. Morgan on the kidneys of Case 4.* The examination was performed 1½ hours after death. Both kidneys were of normal size, and together weighed 275 gm. The capsule stripped readily, leaving a smooth surface. On section, the medulla was very slightly congested, but

otherwise there was no naked-eye evidence of acute, subacute, or chronic nephritis. Microscopic report: 'In sections stained by haematoxylin and eosin there are no unequivocal signs of glomerulo-nephritis in the sense of

### GROUP I CASE I:

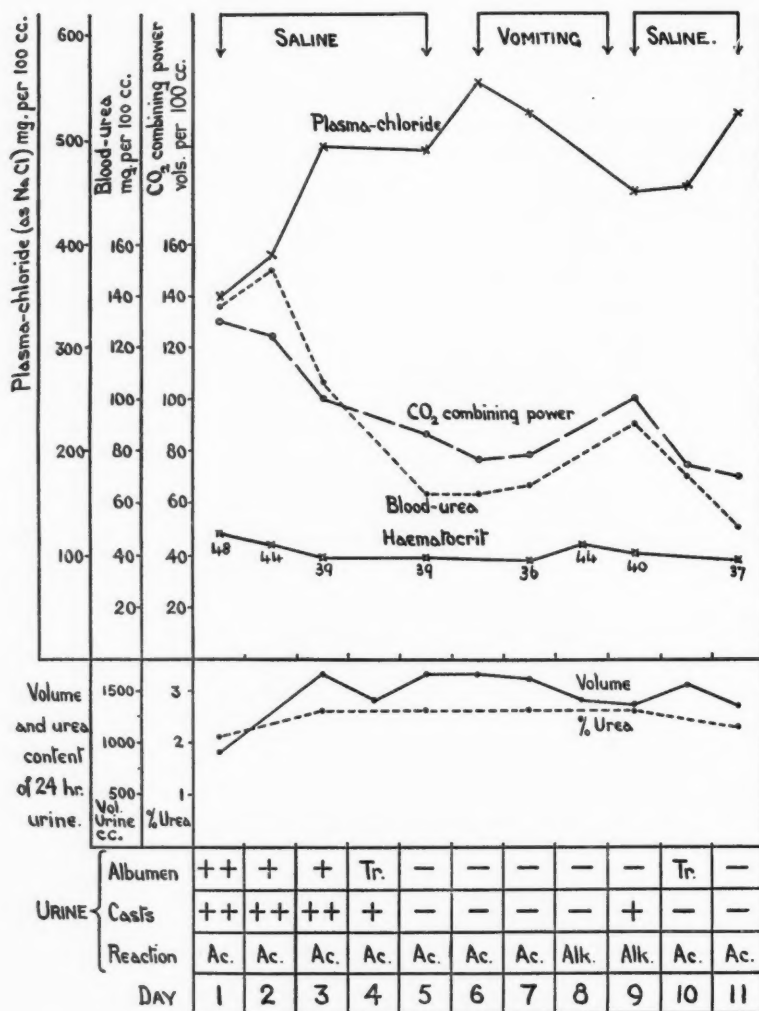


FIG. 1.

an inflammatory lesion. The most striking feature is the universal flattening of the epithelium of the convoluted tubules, in many instances producing a widening of the tubular lumen. The change is uniform, with no resemblance to the alternating areas of tubular dilatation and narrowing found in chronic nephritis. The majority of the tubules contain granular debris, possibly

portions of degenerate epithelium. Staining with Sudan III reveals that the epithelial flattening is more degenerative than atrophic; groups of tubules showing tiny fatty granules crowd the lining epithelium. A few scattered calcium casts are observed. Staining with aniline blue and

### GROUP I. CASE 2.

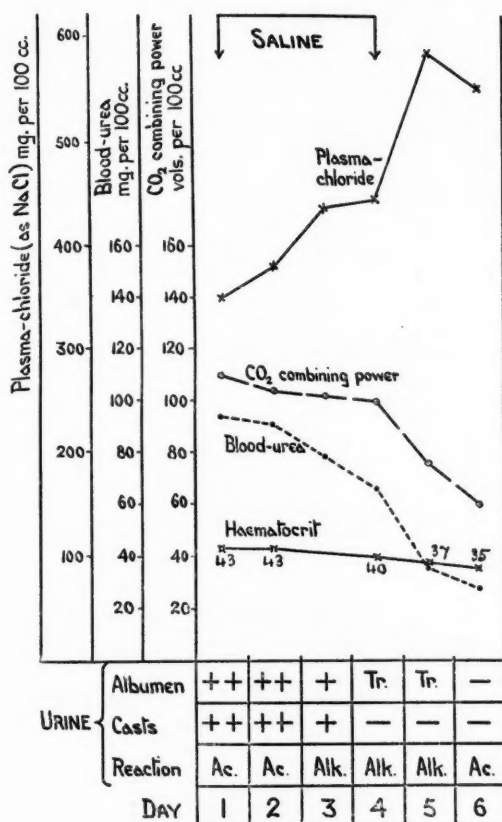


FIG. 2.

orange 6 (Dunn, 1934) shows a tendency to clubbing of the glomerular tufts, with slight thickening of the basement membrane of the glomerular capillaries.'

### Group II. Cases in which Hypochloraemia and Alkalaemia were Produced Experimentally

*Case 5.* A man aged 56 years was admitted to hospital with epigastric pain of duodenal ulcer type, of ten years' duration. He had been vomiting occasionally for almost one year, but never more often than once or twice a week. X-ray examination showed that he was suffering from considerable gastric retention. The chemical composition of his blood was found to be

within normal limits with regard to urea and chloride, but the carbon dioxide combining power was 68 vols. per 100 c.c., a value close to the upper limit of the normal range (54 to 72 vols. per 100 c.c.). He was found to

### GROUP I. CASE 3.

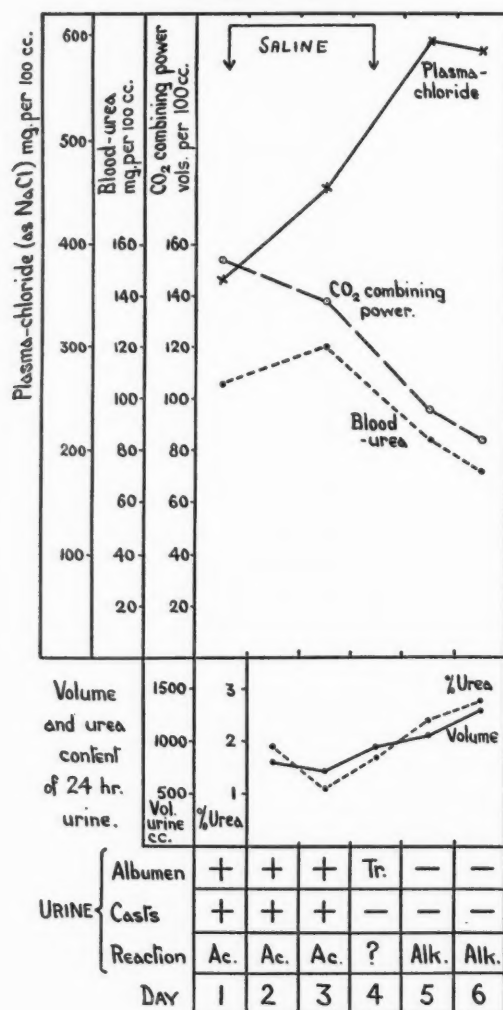


FIG. 3.

have a microcytic hypochromic anaemia. He was not obviously dehydrated, and examination of the blood did not show any evidence of concentration. Occult blood was present in the faeces. The urine did not contain albumen, casts or red blood-cells, and was alkaline in reaction. The gastric acidity was found to be high. After the investigations had been carried out, gastroenterostomy was performed and he made a good recovery (Fig. 5).



Case 6. A woman aged 42 years had suffered from intermittent pain due to duodenal ulcer for twenty-six years. For less than one year she had vomited small amounts of food about once a week. This had been increasing in

GROUP I. CASE 4.

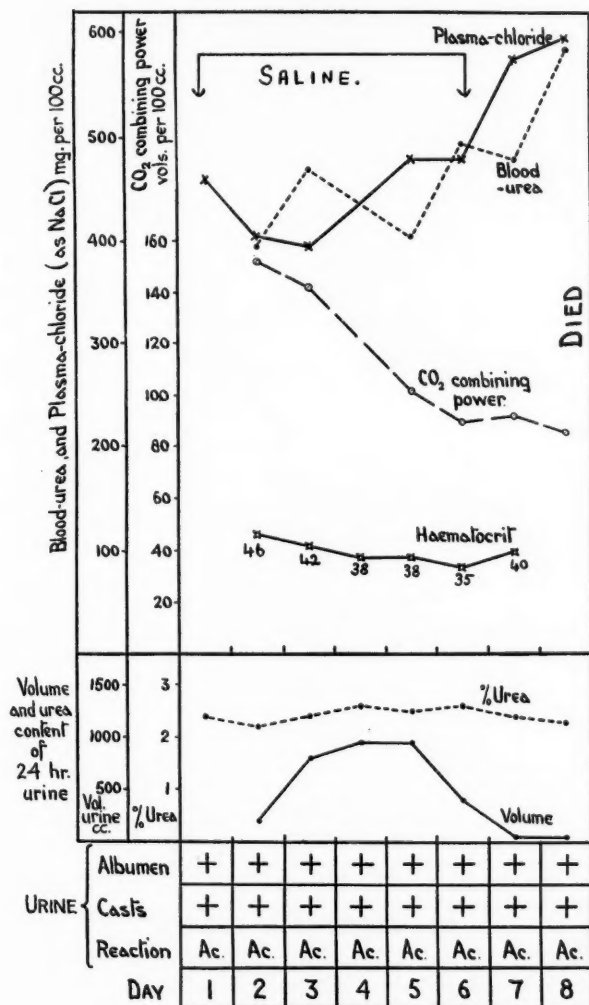


FIG. 4.

frequency for one month before admission to hospital. A test-meal showed considerable gastric retention, but the acidity was within normal limits. The urine was acid in reaction and did not contain any abnormal constituents. The blood showed a slight hypochromic anaemia. She was not dehydrated. After the completion of the tests she made a satisfactory recovery (Fig. 6).

*Case 7.* A man aged 47 years was admitted to hospital after ten years of intermittent dyspepsia, which had previously been proved to be caused by a duodenal ulcer. He had vomited at intervals of three to four weeks for

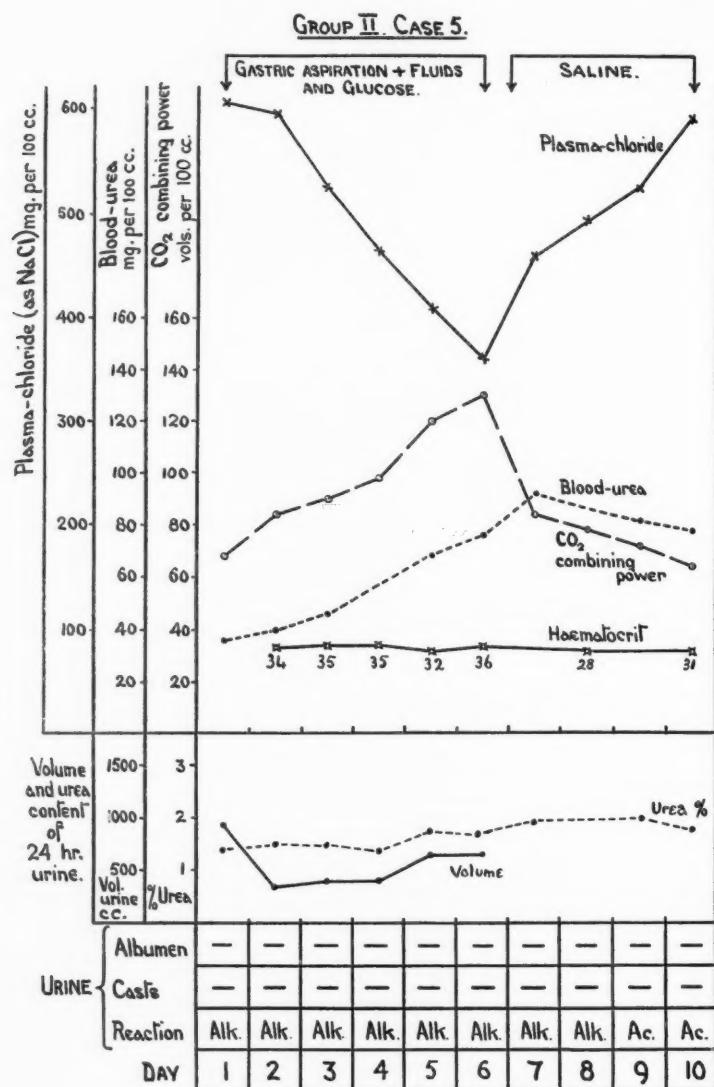


FIG. 5.

one year, but was not dehydrated. He had a high gastric acidity. The plasma-chloride was low on admission (444 mg. per 100 c.c.), but the urea and carbon dioxide combining power were within normal limits (Fig. 7). After the investigations had been carried out he made a satisfactory recovery.

All the patients included in this investigation had been taking baking soda or other alkaline powder to relieve pain for periods varying from two

**GROUP II. CASE 6.**

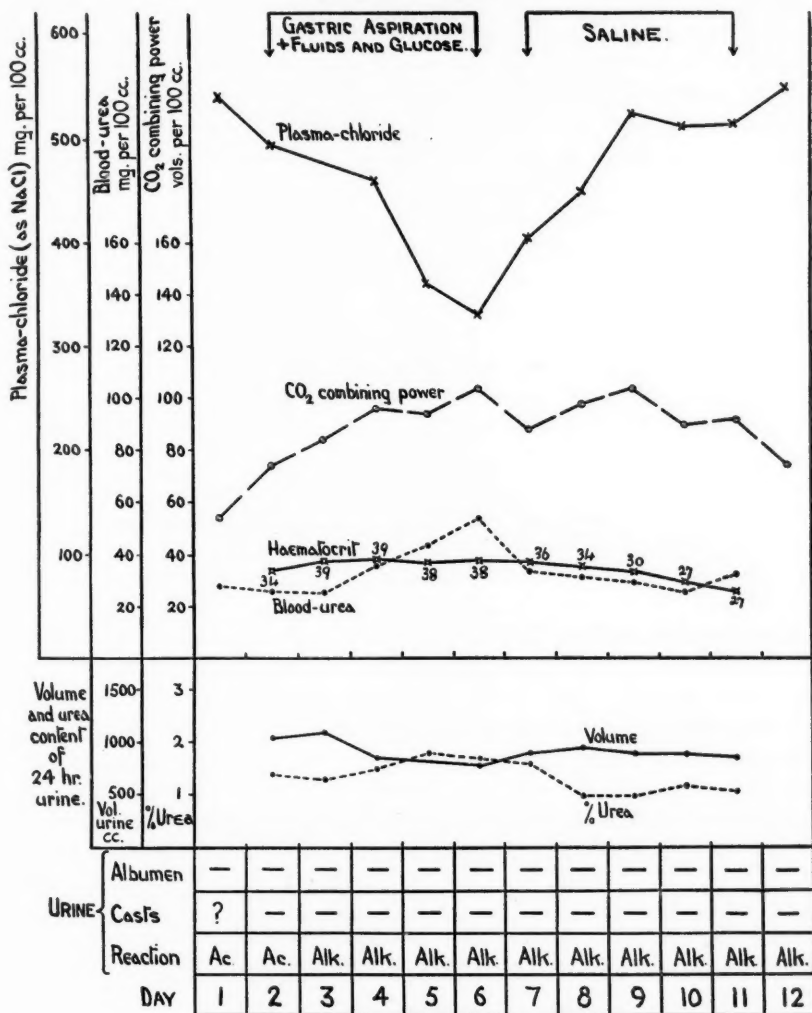


FIG. 6.

to twenty years. It has not been possible to estimate the amounts taken by each patient, as this was dependent on the frequency and degree of symptoms.

*Results.*

The biochemical findings in the cases of Group I are shown in Figs. 1 to 4. In every case the plasma-chloride level on admission was less than 370 mg.

per 100 c.c., the carbon dioxide combining power was over 100 vols. per 100 c.c., and the blood-urea was over 90 mg. per 100 c.c. In all these patients when first seen dehydration was marked, as shown clinically and by blood examination and haematocrit readings.

### GROUP II. CASE 7.

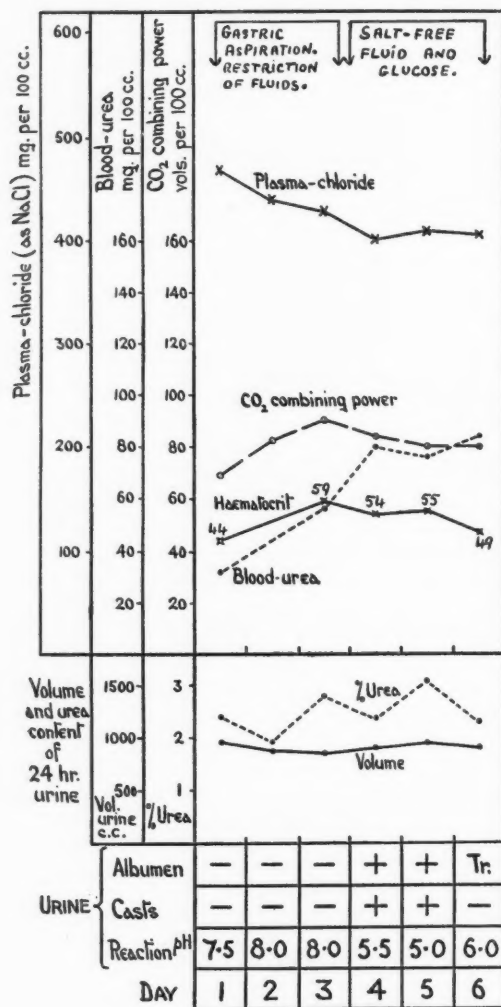


FIG. 7.

The urine in Cases 1, 2, and 3 was acid in reaction and contained albumen, epithelial and granular casts on admission. As the alkalaemia, hypochlor-aemia, and dehydration were corrected by the administration of saline, the albumen and casts disappeared from the urine. It will be seen, from Figs. 1,

2, and 3, that the carbon dioxide combining power of the plasma was still above normal levels after the albumen and casts had disappeared, and that the urine became alkaline in reaction. In Cases 1 and 2 the urine again became acid when the carbon dioxide combining power of the plasma had fallen below 74 and 77 vols. per 100 c.c. respectively. In Case 3 the urine became alkaline after the disappearance of albumen and casts, the carbon dioxide level being 96 vols. per 100 c.c. In this case the carbon dioxide combining power was not observed to fall below 84 vols. per 100 c.c. during the period of strict observation, and the urine did not again become acid in reaction. In Case 4 albumen and casts were persistently present in the urine, and the urinary reaction remained acid in spite of the fact that the carbon dioxide combining power was never lower than 87 vols. per 100 c.c.

In Case 5 (Fig. 5) between  $1\frac{1}{2}$  and  $2\frac{1}{2}$  litres of gastric contents were removed daily for six days, and the intake of salt was restricted. The plasma-chloride fell to 365 mg. per 100 c.c., and the carbon dioxide combining power increased to 130 vols. per 100 c.c. The blood-urea rose only to 80 mg. per 100 c.c., a figure much lower than those found for urea in the dehydrated patients forming Group I at similar levels of the plasma-chloride and alkali reserve. This patient showed no signs of dehydration or haemoconcentration in spite of the loss of chloride, as he was supplied with plentiful fluids ( $3\frac{1}{2}$  to 5 litres daily) by mouth, by rectum, and intravenously. Albumen and casts were not found in the urine throughout the whole experiment. The blood-urea continued to rise until the day after the administration of saline was begun, and thereafter fell slowly, but remained above normal levels until gastro-enterostomy had been performed. The reaction of the urine was alkaline at the beginning of the experiment, when the carbon dioxide combining power of the plasma was 68 vols. per 100 c.c. After correction of the hypochlor-aemia and alkalaemia the urine became acid when the carbon dioxide combining power of the plasma had fallen to 72 vols. per 100 c.c. The volume of urine passed by this patient during the period of gastric aspiration was very small, in spite of the liberal administration of fluids, and in spite of the fact that he showed no sign of dehydration or increase of the haematocrit readings.

Case 6 showed findings similar to those in Case 5. After four days of continuous gastric aspiration and restriction of salt intake, the plasma-chloride had fallen to 336 mg. per 100 c.c., but the urea had risen only to 54 mg. per 100 c.c. In spite of the administration of liberal amounts of fluid, a certain degree of haemoconcentration took place during the period of salt deficiency, although this was never so marked as in the cases forming Group I. The haemoglobin and haematocrit readings increased from 85 and 34 per cent. to 95 and 38 per cent. respectively. The urine did not contain any abnormal constituents throughout the experiment, apart from a few pus cells (the specimens were not always removed by catheter). The reaction of the urine became alkaline when the carbon dioxide combining power of the plasma had risen above 84 vols. per 100 c.c. The volume of urine passed at the

height of salt deficiency and maximum degree of alkalaemia was 780 c.c. in 24 hours.

In Case 7 (Fig. 7) a slight degree of hypochloraemia and alkalaemia existed at the beginning of the experiment. The urine was normal in composition. After the continuous aspiration of gastric contents for two days, combined with restriction of salt and fluids, the alkalaemia and hypochloraemia increased in intensity, and were accompanied by a rise in blood-urea. Haemoconcentration occurred, the haematocrit reading increasing from 44 to 59 per cent. and the haemoglobin from 110 to 130 per cent. The urine became more alkaline in reaction during the first three days while dehydration was increasing, but on the fourth day albumen and casts were found and the urine became acid in reaction. The volume of urine diminished from 960 c.c. in 24 hours, at the beginning of the experiment, to 820 c.c. at the height of dehydration. The administration of salt-free fluid from the fourth day resulted in diminished haemoconcentration, although the plasma-chloride remained low and the carbon dioxide combining power was still high. The azotaemia persisted, in spite of a reduction in the number of casts and albuminuria, and an increased volume of urine. The reaction of the urine became less acid as the albumen and casts disappeared (Fig. 7).

#### *Discussion.*

The patients forming Group I were all severely dehydrated before admission to hospital, and in each case albumen and casts were found in the urine. Albumen and casts disappeared from the urine in Cases 1, 2, and 3 when the volume and chemical composition of the blood were corrected by the administration of saline. In Cases 5 and 6 (Group II) no evidence of structural damage to the kidney, as shown by albuminuria or casts, was observed. Neither of these cases was obviously dehydrated at any time during the investigations. Case 7, in which alkalaemia, hypochloraemia, and dehydration were produced, simultaneously developed albuminuria and cylindruria which became less marked after the administration of fluids, although the alkalaemia and hypochloraemia were maintained. These findings indicate that dehydration is a much more important factor in the production of renal damage than are hypochloraemia and alkalaemia. How it acts is perhaps still uncertain, although it is clear that the structural damage, as illustrated in Case 4, occurs in the tubules (see also Brown, Eusterman, Hartman, and Rowntree, 1923; Cooke, 1933; and others). The likely explanation is, as Fishberg (1939) suggests, that dehydration, causing reduction in blood-volume and increase in blood-viscosity, damages the tubular epithelium by seriously reducing the renal blood supply. Oliguria results, and the urine contains albumen and casts. The same sequence of events is brought about by the dehydration of diabetic coma, where, however, there is acidaemia instead of alkalaemia, and the chloride level is usually normal.

In Cases 5 and 6, where albumen and casts were absent and there was no



significant dehydration (a slight degree of haemoconcentration did occur in Case 6), a rise in blood-urea occurred. This may be a physiological compensation for the loss of chloride, tending to maintain the total osmotic pressure of the plasma unaltered (Hartmann and Smyth, 1926; Wright, 1937). In the dehydrated cases, however, the azotaemia is attributable to renal inadequacy, brought about by the tubular damage already discussed, and by the oliguria resulting directly from the dehydration.

It is seen from the figures that the reaction of the urine was acid in every case while albumen and casts were present in the urine, in spite of very high values for the carbon dioxide combining power of the plasma. The urine of the patients in Group I became alkaline when the albuminuria disappeared after the administration of saline, and when the carbon dioxide combining power was above 74 vols. per 100 c.c. in Case 1, 77 vols. per 100 c.c. in Case 2, and 84 vols. per 100 c.c. in Case 3. In Cases 5 and 6 the urine became alkaline when the carbon dioxide combining power had risen above 73 vols. per 100 c.c. and 84 vols. per 100 c.c. respectively. In Case 7 the urine became alkaline when the carbon dioxide combining power had risen above 69 vols. per 100 c.c., but became acid when casts and albumen appeared in the urine, although the carbon dioxide combining power on this day was 84 vols. per 100 c.c. In Case 4 the urine was acid in reaction during the whole period of observation, although the carbon dioxide combining power was never lower than 87 vols. per 100 c.c. Albumen and casts were present in the urine of this patient throughout the whole of the investigation.

Cases 5 and 6, therefore, behaved like normal subjects, in whom Van Slyke (1917) showed that the urine becomes alkaline when the plasma carbon dioxide combining power exceeds 71.5 vols. per 100 c.c. On the other hand, Cases 1 to 4, with presumed tubular damage, behaved abnormally in secreting an acid urine, while the plasma carbon dioxide combining power was above that level. This finding is in line with Stieglitz's statement that the urine from nephritic kidneys is always acid. It is difficult to reconcile with Rehn's (1925) view, based on purely clinical evidence, that disturbance of renal tubular activity inhibits the excretion of acid radicles, while alkali excretion depends on glomerular function. It seems more likely that tubular damage hampers alkali excretion, though how it should do so is obscure. If that be so, it is obvious that an alkalaemia (as from vomiting or from alkali ingestion), if unaccompanied by dehydration, will tend to be corrected quickly by the physiological excretion of alkaline radicles in the urine; whereas an alkalaemia accompanied by dehydration will tend to persist until dehydration is overcome by the administration of saline (as in Cases 1, 2, and 3), the kidney begins to excrete alkaline urine, and the alkalaemia abates; saline, therefore, is the correct and important treatment, and the administration of acids is unnecessary. The renal damage in these cases is repairable, and the kidneys recover completely normal function. Occasionally, however, as in Case 4, the renal change may advance to an irreversible stage; saline administration then relieves the dehydration and raises the plasma-chloride, but the kidney

continues to produce acid urine containing albumen and casts, the alkalaemia persists, and eventually death occurs in uraemia. It is possible that alkalaemia favours the deposition of calcium in the renal tubules (Fishberg, 1939; Cooke, 1933) and so further impairs renal function.

The practical importance of the observation that a damaged kidney produces acid urine out of an alkalaemic blood is already well known, but bears re-emphasis. Alkalosis is apt to occur in cases of peptic ulcer treated with large or even moderate doses of alkaline powder. Pre-existing renal damage predisposes to it, but is by no means invariably present. When alkalosis occurs, it should be recognized by its symptoms, and it is not excluded by the finding of an acid urine.

### Summary

1. Evidence of renal damage in alkalosis, as shown clinically by the presence of albumen and casts in the urine, was sought in patients suffering from upper intestinal (pyloric) obstruction. All had alkalaemia, hypochlorhaemia, and azotaemia; some were dehydrated, others (in whom the alkalosis was induced experimentally) were not dehydrated.

2. (a) Albumen and casts in the urine occurred in the dehydrated patients, not in the others.

(b) It is therefore suggested that dehydration, haemoconcentration, and consequent impairment of renal blood supply, is the chief mechanism whereby renal tubular damage is produced in alkalosis.

3. (a) Samples of urine containing albumen and casts, passed by the dehydrated patients, were always acid in reaction, notwithstanding considerable alkalaemia.

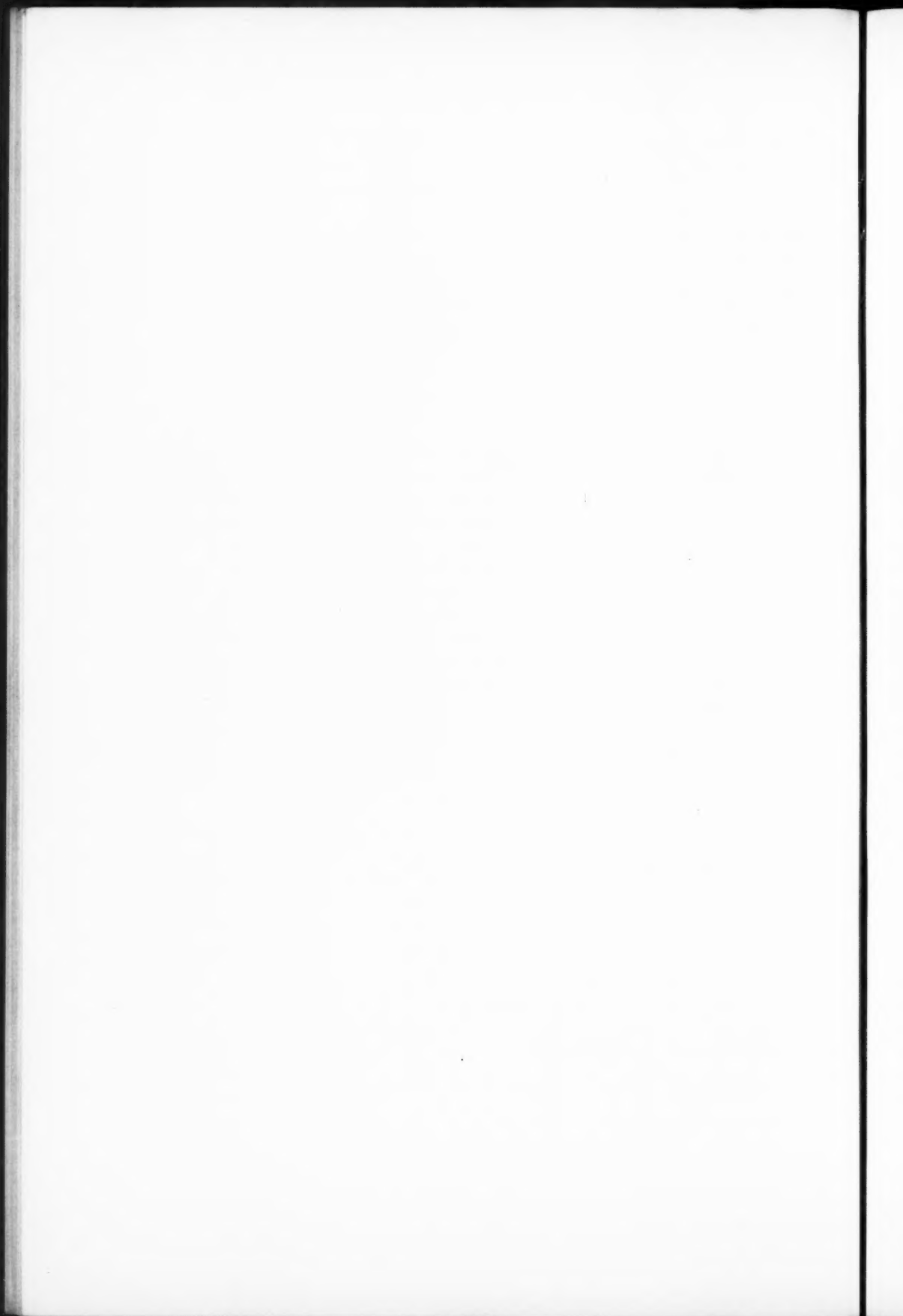
(b) It is therefore suggested that renal tubules, damaged through the above mechanism, fail in their function of secreting alkaline radicles, and thereby aggravate the alkalaemia.

I wish to express my indebtedness to Dr. A. D. Morgan, of the Department of Pathology, Aberdeen University, for carrying out the post-mortem examination on Case 4, for making a careful study of the histological sections of the kidneys, and also for other advice and assistance. I also wish to thank Professor L. S. P. Davidson, Professor J. R. Learmonth, Professor R. S. Aitken, and Dr. A. Lyall for very helpful criticism.

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## THE SERUM CHOLINE ESTERASE IN JAUNDICE AND DISEASES OF THE LIVER<sup>1</sup>

By BRIAN McARDLE

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### *Introduction.*

THE presence in the blood of an enzyme capable of destroying acetylcholine was first suggested by Dale in 1914, but it was not until 1932 that its specificity was demonstrated by Stedman, Stedman, and Easson, and its present name of choline esterase suggested. As the chemical transmitter of a nervous impulse, acetylcholine has received considerable attention from clinicians, but comparatively little interest has been shown in choline esterase. Hall and Lucas (1937) and McGeorge (1937) were unable to correlate the choline esterase activity of the serum with any physiological or pathological condition, except that most of the low values of the former workers were associated with acute infections. Tod and Jones (1937) found the average esterase values to be low in catatonics and high in patients with anxiety neuroses and hyperthyroidism, and tried to correlate these findings with the level of autonomic activity. Low choline esterase values were found by Antopol, Tuchman, and Schifrin (1937, 1938) in jaundice, diseases of the biliary tract, anaemia, and hyperpyrexia. Milhorat (1938) considers low values to be due to debility, a view in which he is supported by Jones and Stadie (1939). In the present study of 269 subjects an association between low choline esterase readings and liver disease has been observed. At the same time no clinical signs or symptoms that could be attributed to a fall in the activity of the enzyme have been noted, and the association remains for the present unexplained. The investigation has been pursued in the hope that the estimation might prove of value in the differentiation of toxic and obstructive jaundice, and as a test of liver function.

### *Method.*

The method used has been that of Jones and Tod (1935). This depends on the measurement in a Barcroft manometer of the amount of carbon dioxide liberated when acetylcholine is added to a mixture of serum and Ringer's solution. The esterase breaks down the acetylcholine to choline and acetic acid, which reacts with the bicarbonate of the Ringer's solution to form carbon dioxide. The concentration of the enzyme is expressed by the volume of carbon dioxide in c.mm. liberated by 1 c.c. of serum in one minute at 37° C. Readings

<sup>1</sup> Received August 30, 1939.

have been taken every two and a half minutes for fifteen minutes. Normally the serum has been diluted one in five. If the concentration of the enzyme is high, the hydrogen-ion concentration changes sufficiently to the acid side to cause partial inhibition of the enzyme. In such cases a one in ten dilution of the serum has been used. Blood taken after venous stasis for five minutes showed on three occasions a consistent increase of 12 per cent. in comparison with that taken without stasis, whilst after stasis for 15 min. there was an equally consistent increase of 16 per cent. Blood was therefore taken with the minimum of stasis.

### *Results.*

*Normal adults.* The choline esterase activity in 40 normal adults has been found to range between 51 and 121 units, with a mean of 78 units. This series agrees well with the figures of Tod and Jones (1937) who in 30 normals and using the same method found a range between 53 and 114, and a mean of 83 units. The normals in the present series have been doctors, research workers, and students. The ages varied from 20 to 52 years, all but seven were between 25 and 35 years, and all but three were males. All previous workers are agreed that the level of serum esterase is unaffected by sex. Hall and Lucas (1935), Verebely (1936), and Antopol, Tuchman, and Schifrin (1937) found that individual normal sera rarely varied by more than 10 per cent., even when observed over a period of months. This has been confirmed in three normal subjects (Table IV) who have been examined repeatedly over a period of two years, one year, and six months respectively, and have all remained remarkably constant, except when an acute infection produced a transient fall in the activity of the enzyme. In the normal group, at least four of the six readings between 50 and 60 units were from persons suffering from mild infections.

*Normal children.* A further group of 20 children has been examined. The observations have been made on children who had come into hospital for minor surgical procedures, or on children who had recovered from the illness that brought them into hospital. They all appeared to be in relatively good health. Their ages varied between 7 and 15 years, and the esterase activity between 71 and 166 units, the mean being 105 units. Only one reading was below 80 units. There was no significant variation between the sexes. This difference from normal adults is statistically significant, but difficult to explain.

*Choline esterase in disease.* The 210 patients examined have been divided into six groups, and the results are summarized in Table I. In all the calculations, and in all the tables included in the text, only the initial values have been used. Most of the choline esterase figures are given in the appendix, the patients being numbered consecutively throughout, but for reasons of space the individual figures in the normal adults, normal children, heart failure, and uraemia groups have been omitted. Some of the patients appear in two or more groups. For instance, the group with definite clinical disease of the



liver is largely composed of patients with cirrhosis, hepatitis, or metastases in the liver, but five cases of jaundice accompanying heart failure or uraemia have also been included. One patient with obstructive jaundice and metastases in the liver is included in both categories. A variable degree of liver damage is likely to accompany heart failure or uraemia, and these have

TABLE I

*Initial Choline Esterase Values in 40 Normal Adults, 20 Normal Children, and 210 Patients.*

Group.	Number of subjects.	Range.	Percentage at 50 units and over.	Mean.
1 Normal adults	40	51-121	100	78
2 Normal children	20	71-166	100	105
3 Miscellaneous	82	13-138	76	71
4 Definite liver disease	71	10-70	21	36
(a) Cirrhosis	23	10-69	26	34
(b) Hepatitis	21	10-70	14	35
(c) Metastases	22	23-61	27	41
5 Heart failure	24	15-98	29	43
6 Uraemia	14	11-70	29	36
7 Hepatic jaundice	38	10-69	13	33
8 Obstructive jaundice	24	34-95	87.5	64

accordingly been classified separately. The hepatic jaundice group has been derived from Groups 4, 5, and 6, whilst the miscellaneous group has been formed by exclusion.

*Definite disease of the liver.* The diagnosis of disease of the liver can sometimes present considerable difficulties. The selection of cases in the present series has been limited therefore to those in which the diagnosis was reasonably certain. A considerable number of the diagnoses were confirmed *post mortem*, and a few at operation. Independent clinical confirmation of the diagnosis has been obtained in every case.

(a) *Cirrhosis.* Eight cases of subacute hepatic necrosis with nodular hyperplasia have been included under this heading. Details of the individual patients are given in Tables VI and IX. The esterase activity of the 23 cases ranged from 10 to 69 units with a mean of 34 units, less than half that of normal adults. All but six (26 per cent.) were below the lowest limit of normal (50 units), and these exceptions will be described more fully than the rest.

*Case 202* had been treated for diabetes for eight years, and had heart failure for three months before her death. Syphilitic aortitis, early biliary cirrhosis, and a very fibrotic gall-bladder containing two stones were found *post mortem*. Choline esterase 53 units.

*Case 203*, a diabetic. Four haematemeses in six years. Had drunk three or more pints of beer a day for many years. Enlarged liver and spleen. Good recovery. Choline esterase 62 units.

*Case 198* had an epithelioma of her palate. Moderately alcoholic. Ascites for one month. Laevulose tolerance test abnormal. Choline esterase 54 units.

*Case 199.* Hypertension and mild heart failure which was not thought sufficient to account for her ascites. Takata Ara test positive. Choline esterase 60 units.

*Cases 184 and 191* had jaundice, and will be discussed under that heading.

(b) *Hepatitis*. There were 21 patients with hepatitis, and all but three had enzyme values below 50 units. Cases 212 and 216 had jaundice and will be described in that section.

*Case 223*. Admitted for vomiting, drowsiness, and abdominal pain. Strong history of alcoholism. Three months later choline esterase 70 units. Liver still much enlarged, but otherwise she was healthy.

In this group as in all others, only the initial value for the choline esterase has been used in calculating the figures of Tables I and II. Full details are given in Tables VII and IX.

(c) *Metastases in the liver*. As might be expected, metastases in the liver had the highest mean value of 41 units, but nevertheless 16 (73 per cent.) of the 22 patients in this group had esterase values below 50 units. As a contrast to this group only 3 (21 per cent.) of the 14 cases of carcinoma examined without liver metastases were below 50 units. Of these three, one had a recto-vaginal fistula and *post mortem* was found to have a fatty liver; another had a carcinoma of the colon, a pelvic abscess, hepatitis, and jaundice; and the third had had unremitting obstructive jaundice for two months.

In all, 71 cases of definite liver disease have been examined. The choline esterase values have ranged between 10 and 70 units with a mean of 36 units. Of these, 56 (79 per cent.) have been below 50 units.

*Obstructive jaundice*. Twenty-one (87.5 per cent.) of the patients with obstructive jaundice (Table X) had esterase figures within the normal limits when first examined. The values ranged from 34 to 95 with a mean of 64 units. This is just significantly lower than the mean for normal adults (Table II). Three cases had values below 50 units.

*Case 226*. Painless jaundice with pale stools for four weeks. Large liver with easily palpable metastases. Diagnosis made of carcinoma of the head of the pancreas with metastases in the liver. Choline esterase 34 units, icterus index 140 units.

*Case 261*. Painless unremitting jaundice for two months. Had lost two stone in weight. Choline esterase 40 units, icterus index 105 units. Died shortly after operation. Blood-urea 540 mg. per 100 c.c. before death. Carcinoma of head of pancreas found *post mortem*.

*Case 265*. Jaundice, pale stools, abdominal pain, and pyrexia for two weeks. Fibrotic gall-bladder full of pigment stones found at operation. Choline esterase 47 units, icterus index 65 units.

If the obstruction persists for long, liver damage may be expected to supervene, and the choline esterase to fall. This occurred in four cases whilst under observation.

*Hepatic jaundice*. Thirty-eight cases have been examined, in most of which the jaundice has been mild, the icterus index in 24 cases being 40 units or less. The esterase value has varied between 10 and 69 units (Table IX), with a mean of 33, and in only 5 cases (13 per cent.) was it above 50 units. In 28 (74 per cent.) it was below 40 units. Brief details are given of the five cases with values over 50 units.

*Case 184.* Weakness with loss of weight for eight months, ascites for three weeks, and jaundice with clay-coloured stools for three days. Liver enlarged and irregular. Diagnosed as cirrhosis. Choline esterase on admission 54 units, one month later 27 units. Icterus index 40 units. Died two months later. No post mortem examination.

*Case 205.* Moderately severe lobar pneumonia with mild jaundice that cleared up rapidly after the crisis. Esterase activity was 53 units during the jaundice; 10 days later when she had recovered it was 97 units.

*Case 191,* a young man of 19 years, in Oct. 1937 was seized with a colicky midline abdominal pain persisting for one night and followed by jaundice with pale stools and dark urine. The jaundice lasted about four weeks. In July 1938 he again developed jaundice with pain, nausea, pruritus, pale stools, and dark urine. The jaundice persisted until Oct. 1938 when he was admitted to hospital. Moderate jaundice which rapidly improved. His liver became smaller and less tender. No fever. Prompt direct van den Bergh reaction, Takata Ara reaction positive, and the laevulose tolerance test showed a mild degree of liver damage. The choline esterase (69 units) was not estimated until the jaundice had almost gone. The case was under the care of Dr. Donald Hunter who diagnosed subacute hepatic necrosis.

*Case 216.* An insect bite on the hand was followed by swelling of the hand, diarrhoea, and vomiting which persisted until mild jaundice developed four days later. The esterase was 53 units on the first day of the jaundice, 51 units two days later, and when he was fully recovered 18 days later it had risen to 71 units. The icterus index did not rise above 35 units. Van den Bergh reaction biphasic; urobilinogen present in the urine.

*Case 232,* a woman of 62 years had had painless jaundice, pruritus, and clay-coloured stools for two weeks, poor appetite and loss of weight for one month. Choline esterase 61 units, icterus index 110 units. At operation a few metastases were found in her liver. No primary carcinoma found.

In a number of instances it was possible to follow the esterase value during the course of the disease, and in the majority it proved a reliable index of the clinical state of the patient. Cases 204 and 207 were followed at frequent intervals over a period of time.

*Case 204,* a man aged 30 years, developed jaundice after influenza three weeks before his admission to hospital. His stools were pale and his urine dark. A week later he developed oedema of his legs, and this was present on admission. On examination he was moderately jaundiced and his liver was tender and enlarged one inch below the costal margin. For the first month, although his jaundice improved, his clinical condition deteriorated; the oedema became generalized, and he developed ascites, six pints of fluid being withdrawn. The plasma-albumin fell at this time to 0.78 gm. per 100 c.c. No albumin in the urine. Then for three weeks his condition remained unchanged, but recovery thenceforward was rapid. His liver was enlarged both on discharge and one year later, although he was symptomless and in good health. The choline esterase values approximately reflected the clinical condition in this case, being 20 units on admission, falling to 12 units and rising with improvement first to 40 units and then to 60 units. The case was under the care of Professor Ryle who diagnosed subacute hepatic necrosis.

*Case 207,* a man aged 62 years was admitted to Addenbrooke's Hospital on 27.7.38, with a three weeks' history of painless jaundice, pale stools, and dark urine. In August 1937 and March 1938 he had had similar though less severe attacks of jaundice lasting about two weeks. He was thin and markedly

jaundiced, but in other respects healthy. His liver was enlarged one and a half inches below the costal margin; its surface and edge were irregular. His spleen became palpable three weeks later. He made an uninterrupted recovery. The esterase content rose with the clinical improvement from 25 units to 43 units. He was under the care of Professor Ryle who diagnosed a toxic hepatitis. He was seen again on 21.10.38. He was no longer jaundiced, had put on weight, and the esterase was 53 units. In February 1939 he was symptomless, and seemed in very good health apart from the fact that his liver and spleen were both palpable. His choline esterase was unchanged at 52 units.

In this man the test, whilst reflecting accurately the course of the jaundice, failed to show the persisting cirrhosis of which the enlarged liver and spleen were taken as evidence. In a few patients the choline esterase had returned to normal limits before the jaundice had entirely cleared up. Case 214, a young man with one month's history of jaundice following arsenical injections, was an example of this. On the whole it can be said that the lower the esterase value, the more severe the liver damage, but this is not absolute, as a figure of 39 units was found in the case with the most severe damage of the series (Case 209). In view of the considerably higher range of values in normal children, two cases of mild jaundice occurring in young boys have been omitted from this series.

*Heart failure and uraemia.* In these two groups, and especially in the latter, it is difficult to assess the degree of liver damage present. Both included cases of all degrees of severity, and here again the low esterase value usually corresponded with the more severe illness. A case of severe heart failure with an esterase of 98 units was a notable exception to this generalization.

*Miscellaneous cases.* The miscellaneous group included a wide range of diseases (Table V), and there was an equally wide range of choline esterase values, the highest being greater by ten times than the lowest. Neither the mean value of 72 units when all the cases in this group are considered, nor the mean value of 70 units when the 15 patients under 20 years are excluded, is significantly lower than the mean for the normals. Twenty patients at some stage of their illness had values below 50 units. During recent years the wide variety of diseases and infections in which liver function is impaired has become increasingly appreciated. Impairment has been found commonly in pneumonia by Curphey and Solomon (1938); in anaemia by Barker (1938) and Fouts, Helmer, and Zerfas (1937); in hyperthyroidism by Bartels (1938), Maddock, Petersen, and Coller (1937), and Boyce and McFetridge (1938 *b*); in acute rheumatism by Bland and Jones (1938); and in moderate to advanced tuberculosis by Levinson and Seigal (1938). Twelve of the 20 cases in the miscellaneous group with values below 50 units were instances of these diseases, and in one other there was post-mortem evidence of liver damage.

*Statistical summary.* A statistical survey of the choline esterase data is given in Table II. The figures have been obtained by methods outlined by Hill (1937). The last column gives the 'significance' of the difference of the mean of the group from the normal mean of 78 units. The difference is said

to be statistically 'significant' (that is, unlikely to arise by chance) if the 'significance' is greater than 3.

From the table it can be seen that there are statistically significant differences from the normal adult mean in all groups except the miscellaneous. The mean value in the obstructive jaundice group is just statistically different

TABLE II

*Statistical Summary of the Results. (Initial Values only.)*

Group.	Number of cases.	Range.	Mean.	Standard deviation.	Coefficient of variation.	Standard error of mean.	Standard error of difference from normal mean.	Significance.*
Normal adults	40	51-121	78	17.0	21.8	2.7	—	—
Normal children	20	71-166	105	24.1	22.9	5.4	5.9	(4.6)
Miscellaneous†	67	13-124	70	26.5	37.9	3.2	4.2	1.9
Definite liver disease	71	10-70	36	15.6	43.4	1.9	3.3	12.8
Cirrhosis	23	10-69	34	22.0	64.7	3.8	5.3	(8.3)
Hepatitis	21	10-70	35	14.3	40.9	3.1	3.6	(11.9)
Metastases in liver	22	23-61	41	8.9	40.5	1.9	3.3	(11.2)
Heart failure	24	15-98	43	17.6	41.0	3.6	4.5	(7.8)
Uraemia	14	11-70	36	17.0	47.1	4.5	4.6	(9.1)
Hepatic jaundice	38	10-69	33	13.2	40.0	2.1	3.4	13.2
Obstructive jaundice	24	34-95	64	14.7	23.0	3.0	4.0	(3.5)

\* A difference is unlikely to have arisen by chance if the 'significance' is above 3. Brackets have been placed round the figures in those groups with less than 30 cases.

† Patients under 20 years of age have been excluded from this group.

from the adult normal mean, whilst it is extremely improbable that the difference of the mean value of the hepatic jaundice group could have arisen by chance. Although not included in the table, the difference between the two jaundice groups of 31 units is statistically significant (standard error of the difference of the two means 3.7, significance 8.4). Brackets have been placed in the 'significance' column around the figures of those groups containing fewer than 30 patients, as these groups are rather small. Patients under the age of 20 years have been omitted from the miscellaneous group to make it comparable with the normal adult group. The choline esterase values of the 15 patients under 20 years of age ranged from 53 to 138, with a mean of 79 units.

*Effect of dialysis on sera with low activity.* Antopol, Tuchman, and Schiffrin (1938), and Sobotka and Antopol (1937) have suggested that the low values which they found in diseases of the biliary tract might be due to the presence in the serum of some substance capable of inhibiting the activity of the enzyme. They suggested bile salts as a possible inhibitor. Should such a substance be present, it might be possible to remove it by dialysis. Accordingly serum with an enzyme activity of 46 units was dialysed in a cellophane bag against running water for 24 hours. The choline esterase fell to 41 units. Another sample of 2 c.c. of serum with an enzyme activity of 30 units was diluted with 20 c.c. of normal saline and dialysed in a collodion sac under pressure against normal saline for 48 hours until the original volume of 2 c.c. was restored. The enzyme activity had fallen to 26 units.



*Discussion*

Previous workers, with the exception of Antopol, Tuchman, and Schifrin (1938), have not linked low choline esterase values with liver disease. This may be due to the small number of cases of primary liver disease examined and the variety of disorders which may temporarily injure the liver. Jones and Stadie (1939) found a mean choline esterase value of 41 units in both advanced pulmonary tuberculosis with extreme emaciation and advanced carcinoma with marked cachexia. Vahlquist (1935) also found low values in advanced tuberculosis. Using the bromsulphalein test of liver function Levinson and Seigal (1938) have shown that liver function is impaired in 57 per cent. of cases of moderate to advanced tuberculosis. Tod and Jones (1937) in six cases of catatonia found a mean choline esterase activity of 46 units. Quastel and Wales (1938) using the hippuric acid synthesis test of Quick (1933) found some degree of impairment of this function of the liver to be present in all the 18 cases of catatonia examined, though Ström-Olsen, Greville, and Lennon (1938) found it present only in five out of 28 cases.

Antopol, Tuchman, and Schifrin (1937) associated low values with jaundice, diseases of the biliary tract, anaemia, and hyperpyrexia. In a later paper (1938) they stressed the association with biliary tract disease, and advanced the hypothesis that the low figures found might be due to bile salt retention, which they showed inhibited the enzyme *in vitro*. Evidence against this hypothesis is afforded by the normal values encountered in the present series of cases of obstructive jaundice, and the failure to remove an inhibiting factor by dialysis. Nor do their own figures provide support for their theory. Sixty normal sera were examined by a method different from that used in this series, and with a different unit of activity. The figures for the normals ranged from 31 to 99 units, with a mean of 67.6. Twenty-one cases of jaundice were examined. Of the 10 cases with choline esterase values below the normal range, nine were cases of hepatic jaundice, the other one being a case of acute haemolytic icterus with an icterus index of 12 units, a choline esterase of 29 units, and a haemoglobin of 30 per cent. Six of the 11 cases within the normal range were patients with undoubted obstructive jaundice, two were cases of catarrhal jaundice who, judging by the icterus indices (13 and 18 units), had either had a mild attack or were almost recovered. One of these two cases was a child of 8 years, and I have shown children to have higher choline esterase values than adults. The cause of the jaundice in the other three cases was not clear. Although they do not suggest it in any way as a test for differentiating jaundice, their figures provide confirmatory evidence of the value of choline esterase determinations in the differential diagnosis of jaundice. Milhorat (1938) and Jones and Stadie (1939) considered debility to have been the cause of their low esterase values. Whilst debility was present in a large proportion of my cases with low choline esterase values, there have been a number of patients in which debility was not present. Conversely a number of those with normal choline esterase



values were debilitated. The correlation of low values with liver disease was much closer.

*The causes of low choline esterase activity.* In the absence of sufficient data, no attempt will be made to theorize as to the many possible causes for the fall that occurs in diseases of the liver. It has not been found possible to

TABLE III

*A Comparison of Choline Esterase Results with those of some other Liver Function Tests.*

Test.	Authors.	Number of cases.	Number of positive results.	Percentage of positive results.
Laevulose tolerance test	Kimball (1932)	142	81	57
	Soffer (1935)	70	38	54
(Estimation of total blood-sugar)	Stewart, Scarborough, and Davidson (1938)	43	24	56
Laevulose tolerance test	Stewart, Scarborough, and Davidson (1938)	59	45	75
(Estimation of blood-laevulose)	Herbert and Davison (1938)	38	31	82
Bromsulphalein test	Soffer (1935)	52	32	62
	Cornell (1929)	51	26	50
	O'Leary, Greene, and Rown-tree (1929)	67	54	80
Bilirubin tolerance test	Soffer (1935)	72	62	86
Hippuric acid synthesis test	Quick (1936)	37	33	89
Choline esterase test		71	56	79

demonstrate an inhibiting substance in the serum or liver by mixing normal and abnormal sera, or by mixing an aqueous extract of the liver from a case of acute hepatic necrosis, with normal serum. The inhibiting substance, should there be one, is not dialysable. The choline esterase values of two livers from cases of acute hepatic necrosis were less than half those from two normal livers. No choline esterase activity was found in the urine from a case of toxic hepatitis.

*A comparison with some other tests of hepatic function.* The choline esterase has been found abnormal in 79 per cent. of 71 patients who have had either cirrhosis, hepatitis, metastases in the liver, jaundice the result of cardiac failure, or uraemia. The results compare favourably with those published for other liver function tests. For purposes of comparison some typical results of these other tests have been summarized in a table.

Kimball (1932) using the laevulose tolerance test found it to give correct results in 81 (57 per cent.) of 142 cases of disease of the liver, whilst Soffer (1935) in 70 similar cases observed abnormal curves in 38 (54 per cent.). This test has recently been modified and improved by determining the blood-laevulose rather than the total sugar. Stewart, Scarborough, and Davidson (1938) found this test to give abnormal curves in 45 (75 per cent.) of 59 cases of liver disease. Analysis of their data shows that the original laevulose tolerance test gave 24 (56 per cent.) positive results in 43 patients (omitting diabetics)

with disease of the liver. It should be pointed out that using the same criteria, four of the 10 normal subjects over 50 years showed evidence of liver damage, as judged by the total sugar curves. With the new test Herbert and Davison (1938) in 38 cases found 7 (18 per cent.) to give normal curves, 8 (21 per cent.) 'high normal' curves, and 23 (61 per cent.) abnormal curves.

The bromsulphalein test seems to give between 50 per cent. (Cornell, 1929) and 80 per cent. (O'Leary, Greene, and Rowntree, 1929) accuracy in diagnosis, depending on the technique, the standards of normality employed, and the type of cases studied. Soffer (1935) using 5 mg. of dye per k. of body weight, in a representative series of 52 cases of hepatic disease found 32 positive, or 62 per cent. accuracy.

The bilirubin tolerance test is probably the most delicate test of liver function, Soffer (1935) finding it accurate in 86 per cent. of 72 patients with mild liver damage. In 18 cases in which it was compared with the bromsulphalein test it gave 89 per cent. accuracy, whilst the bromsulphalein test was positive only in 17 per cent. Unfortunately, it cannot be used in cases of jaundice, it is very expensive, and considerable caution must be exercised in carrying out the test.

Probably the most satisfactory of these other tests is the hippuric acid synthesis test of Quick (1933, 1936). This test depends on the ability of the liver to conjugate benzoic and amino-acetic acid to form hippuric acid, which is excreted and estimated in the urine. It has been commented on favourably by Snell and Magath (1938), Boyce and McFetridge (1938 *a*) and others, but the presence of dehydration, malnutrition, renal injury, or impaired intestinal absorption may lead to fallacious results. The intravenous instead of the usual oral administration of the drug (Quick, Ottenstein, and Weltchek, 1938) obviates the last difficulty.

It would seem then that as an index of liver function, the determination of choline esterase in the serum is probably rather more sensitive than the old laevulose tolerance and bromsulphalein tests, about equal to the new laevulose tolerance test, and somewhat less sensitive than the bilirubin tolerance and the hippuric acid synthesis tests.

*A comparison with some other differential tests of jaundice.* It is very doubtful if it will ever be possible to select any one test that will give absolute accuracy in the differentiation of toxic and obstructive jaundice. Cases of toxic jaundice have frequently an intrahepatic obstructive element, and cases of obstructive jaundice persisting for any length of time develop some degree of liver damage. To be of value in jaundice, therefore, a test dependent on the measurement of liver function must be sensitive to the diffuse liver damage usually found in toxic jaundice, and relatively insensitive to the more local type of injury found in biliary obstruction. Judging by the results, it is likely that the determination of the choline esterase possesses these features to a considerable degree. Although a number of the values have been close to the dividing line of 50 units, there

has usually been no difficulty in deciding the true type of jaundice when these values were taken in conjunction with the clinical findings.

There is need for a more reliable test than exists at the moment. The van den Bergh test is of limited value. Reports on the value of the serum-phosphatase are conflicting, ranging from those of Greene, Shattuck, and Kaplowitz (1934) who consider it to be of very little value, to those of Roberts (1933) who found it accurate in 98 per cent. of 52 cases, and of Rothman, Meranze, and Meranze (1936) who in 53 cases found it to give an 87 per cent. accuracy. From the literature it would seem that the galactose tolerance test gives an 80 to 90 per cent. accuracy in diagnosis (Worner, 1919; Soffer, 1935; Owen, 1934; Schiff and Senior, 1934), though Banks, Sprague, and Snell (1933) were able to obtain only a 57 per cent. accuracy in 99 cases. The laevulose tolerance test is sometimes used in the differentiation of jaundice, but analysis of the data of Stewart, Scarborough, and Davidson (1938) reveals its value in this respect to be negligible. In 33 cases of jaundice, 52 per cent. accuracy was obtained by estimating the blood-laevulose, whilst the total sugar curves in 30 cases gave only 37 per cent. accuracy. It was particularly apt to be wrong in obstructive jaundice, nine out of 13 patients giving abnormal laevulose curves, and 10 out of 12 giving abnormal total sugar curves. The Takata Ara test or one of its modifications is of definite but limited value in the diagnosis of jaundice, a positive result being very much in favour of the diagnosis of cirrhosis or toxic jaundice, although a negative reaction does not rule out toxic jaundice. Sommer (1937) in 585 cases of jaundice found it to be positive in 180 of 366 cases of parenchymatous injury, but only in 20 of 194 cases of obstructive jaundice, and in these, associated liver damage was present.

The hippuric acid synthesis test, whilst of value in assessing the degree of damage in cases of jaundice, does not appear to be of much value in differential diagnosis. Snell and Magath (1938) and Boyce and McFetridge (1938 *a*) were very much of this opinion, although Quick (1936) considered it of value. However, there were only four instances of obstructive jaundice in his series, and it is in this group particularly that the other workers found it to give fallacious results.

*Certain features of the test.* The dependence on the preparation of the patient, absence of vomiting, efficient absorption, and adequate collection of samples are small but sometimes real disadvantages in some of the more popular liver function tests. A single venepuncture without undue stasis is all that is required for the determination of the choline esterase content of the serum. It can be done on any patient at any time, and as often as is necessary. The sample of serum preserved with a little chloroform will keep for months. The determination is simple, provided a Barcroft or Warburg manometer is available, and there are simpler, though possibly not quite such accurate methods (McGeorge, 1937) of determining the concentration of esterase in the serum.

Certain obvious considerations must be weighed against these advantages.

In the first place the test at present is empirical, and as such demands a closer scrutiny than would be accorded to one having a known physiological basis. Although it gives a fair approximation of the degree of liver damage, it is not always sufficiently sensitive to show the presence of a pathological liver in the late recovery stages of toxic jaundice or in mild hepatitis. In prolonged obstructive jaundice and in cholecystitis an associated hepatitis is common, and the choline esterase might well give poor results in a series in which these cases predominated. The same may be said of any test which in the differentiation of jaundice depends on the measurement of liver function. Antopol, Tuchman, and Schifrin (1937) have shown that the choline esterase is higher than normal in hyperthyroidism, and possibly in diabetes. The data in the present series whilst suggestive, do not definitely support their contention, but some of the thyrotoxic patients had received treatment before the determination was made, and this had been shown to lower the esterase content. Glick and Antopol (1939) tentatively suggested that vitamin B<sub>1</sub> deficiency might be the cause of the abnormal values in these two conditions, but they were unable to obtain proof, and in view of the high figures in children, an endocrine abnormality must also be considered. From the point of view of the present paper, the importance of these high figures lies in the possibility of fallacious results being obtained when these conditions co-exist with liver disease. It is worthy of comment that two of the six cases of cirrhosis with values above 50 units had diabetes.

Most of these difficulties can be minimized if the test is used in conjunction with the clinical findings and if other tests are employed at the same time. In jaundice the galactose tolerance test would tend to be at fault in the same type of case as the choline esterase test, and for that reason the phosphatase test might prove most useful. In disease of the liver the hippuric acid synthesis test is likely to be of most value. In view of the ease with which the Takata Ara test can be performed and of the significance of a strongly positive result, it is worth employing it in either condition. Repeated determinations of choline esterase activity at intervals of a few days may sometimes clear up a diagnosis, when one determination has left it in doubt.

#### *Summary*

- (1) The choline esterase has been determined in the serum of 270 subjects.
- (2) In 40 normal adults the range was from 51 to 121 units, with a mean of 78 units. For children (7 to 15 years old) the values varied from 71 to 166 units, the mean being 105 units.
- (3) In diseases of the liver the values were much lower. Of the 71 cases examined, 79 per cent. were below 50 units, the range being from 10 to 70 units, and the mean 36 units. This difference from normal adults is statistically significant.
- (4) Eighty-two patients with miscellaneous diseases had esterase values between 13 and 138, with a mean of 71 units. Twenty had values below 50

units, and in many of them there were strong clinical indications of liver damage.

(5) The initial figure for choline esterase was 50 units or above in 21 (87.5 per cent.) of the 24 instances of obstructive jaundice, whilst in jaundice of hepatic origin it was below 50 units in 33 (87 per cent.) of the 38 cases. Improvement or impairment of liver function was accompanied by a rise or fall respectively in choline esterase.

(6) It is suggested that the determination of the choline esterase in the serum might usefully be employed both as a measure of liver function and as a test in differentiating jaundice of hepatic and obstructive origin. A value below 50 units indicates that the liver is damaged.

(7) Normal figures in hyperthyroidism and possibly in diabetes may not necessarily mean a healthy liver.

(8) The test compares favourably with other tests used in the diagnosis of jaundice and disease of the liver.

(9) It is emphasized that, as with all other function tests, it is likely to be of most value when used in conjunction with the clinical findings.

(10) The results have been subjected to statistical analysis.

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## APPENDIX

To save space individual details of the normal adults and children (Nos. 1 to 60), and of the patients with heart failure (Nos. 143 to 166) and uraemia (Nos. 167 to 180) have not been given. The mean blood-urea of the patients with uraemia was 293 mg. per 100 c.c.

TABLE IV  
*Individual Variations in Choline Esterase.*

Case 4. Date.	Choline esterase units.	Case 7. Date.	Choline esterase units.	Remarks.	Case 24. Date.	Choline esterase units.	Remarks.
7.3.37	65	20.5.38	98		14.10.38	55	Bad cold
27.4.37	66	2.11.38	102		29.11.38	104	
28.5.37	51	3.11.38	101		1.12.38	107	
25.6.37	66	4.11.38	101		9.2.39	105	
21.3.38	70	5.11.38	96		6.3.39	97	
2.11.38	78	6.11.38	98		7.3.39	101	
3.11.38	72	7.11.38	101		9.3.39	98	
4.11.38	77	8.11.38	97		28.3.39	96	
5.11.38	76	9.11.38	103				
6.11.38	76	10.11.38	98				
7.11.38	77	11.11.38	98				
8.11.38	76	1.12.38	107	Mild influenza			
9.11.38	74	7.2.39	93				
10.11.38	77	28.2.39	101				
11.11.38	76	6.3.39	107	Sore throat			
8.12.38	75	9.3.39	93	Sinusitis			
13.12.38	76	14.3.39	89	Sinusitis			
9.2.39	76	16.3.39	94	Recovering			
28.2.39	74	21.3.39	89	Recovered			
		24.3.39	102				

TABLE V  
*Miscellaneous Cases.*

Case No.	Disease.	Choline esterase units.	Remarks.
*61	Pink disease	138	
62	Obesity	124	
63	Asthma	118	
64	Thyrotoxicosis	114	
65	Exophthalmic ophthalmoplegia	113	
66	Chronic cholecystitis	111	Mild
67	Myasthenia gravis	111	
*68	Rheumatic fever	108	
*69	Pink disease	107	
70	Cerebral haemorrhage	106	
71	Diabetes	105	
72	Thyrotoxicosis	103	
73	Urticaria	97	
74	Hyperparathyroidism.	96	
75	Thyrotoxicosis	96	
76	Cataplexy	94	No change during an attack
77	Alcoholic neuritis, pulmonary tuberculosis	93	
*78	Myasthenia gravis	92	
79	Hour-glass stomach. Alkalosis	92	
80	Urticaria	89	
81	Paroxysmal auricular fibrillation	88	



TABLE V (continued)

Case No.	Disease.	Choline esterase units.	Remarks.
82	Diabetes	88	Clinically no metastases
83	Carcinoma of the rectum	87	
84	Asthma	87	
85	Thyrototoxicosis	85	
86	Diabetic neuritis; splenomegaly (cause unknown)	84	
87	Thyrototoxicosis	83	
88	Diabetes	83	
89	Familial periodic paralysis	81	No significant change during attack
90	Fibrositis	81	
*91	Tonsillitis	81	
92	Thyrototoxic myopathy	80	
93	Diabetes; alcoholic neuritis	78	
*94	Rheumatic fever	78	
95	Rheumatoid arthritis	77	
96	Myasthenia gravis	77	
97	Thyrototoxicosis	74	Mild
98	Familial periodic paralysis	72	No significant change during attack
99	Urticaria	73	No change during an attack
100	Rheumatoid arthritis	71	
*101	Diabetic coma	71	
102	Erb's juvenile myopathy	71	
*103	Puberty goitre	70	
104	Hypertensive auricular fibrillation	69	
*105	? Simmonds' disease	69	
106	Adrenal carcinoma, multiple secondary deposits	69	Post mortem, no metastases in the liver
*107	Rheumatic fever	69	
108	Asthma	69	
109	Rheumatic pericarditis	67	
110	Carcinoma of the pancreas	66	Clinically no metastases
111	Chronic lymphatic leukaemia	66	
112	Duodenal ulcer	64	
113	Urticaria	7.4.37 14.4.37	Urticaria unchanged
		43	
114	Myasthenia gravis	62	
*115	Tabes mesenterica	62	
116	Urticaria	60	
*117	Lymphatic leukaemia	59	
118	Polycythaemia	57	
119	Pyelitis	55	
120	Thyrototoxicosis	53	Severe
*121	Rheumatic carditis	53	
122	Carcinoma of the oesophagus	50	Post mortem, no metastases
123	Pernicious anaemia	49	Hb. 43 per cent.
124	Lobar pneumonia	48	
*125	Anorexia nervosa	47	Semi-comatose, very emaciated
127	Hypochromic anaemia	47	Hb. 30 per cent.
128	Lobar pneumonia	21.9.38 27.9.38 1.10.38 12.10.38	Second day of illness Crisis Recovering Recovered
129	Obscure anaemia (? aplastic)	44	Hb. 43 per cent. Purpura
130	Pyloric stenosis, recent alkalosis, and gastrojejunostomy	41	Also anaemic and asthmatic
131	Pernicious anaemia	39	Hb. 30 per cent. Confused mentally

TABLE V (continued)

Case. No.	Disease.	Choline esterase units.	Remarks.
132	Haematemesis	36	Blood-urea 160 mg. per cent.
133	Severe rheumatic fever	34	Very ill
		43	Improving
		61	Recovered
		65	Healthy
134	Thyrotoxicosis, auricular fibrillation		
		34	
		23	Two days after partial thyroid-ectomy
		51	Improved
		47	Recovered, but still fibrillating
135	Pernicious anaemia, subacute combined degeneration	33	Mentally confused
136	Lobar pneumonia	32	Transient diabetes
137	Tuberculous peritonitis and enteritis	31	
138	Lobar pneumonia	30	Alcoholism
139	Pyloric stenosis	30	Alkalosis, tetany
		57	Fully recovered
		57	
140	Rheumatoid arthritis	23	Active
		21	Quiescent
		27	Quiescent
		17	<i>Post mortem</i> , showed well marked fatty changes
141	Carcinoma of the uterus, recto-vesical fistula		
142	Large bilateral renal calculi and pyonephroses		
		13	Great asthenia. B.P. 75/25
		30	Some improvement

\* Not included in the statistical analysis as age was under 20 years.

TABLE VI

*Cases of Hepatic Cirrhosis.*

Details of the cases of cirrhosis with jaundice (Nos. 181 to 192) are given in Table IX of the Appendix.

Case No.	Remarks.	Choline esterase units.
193	Subacute hepatic necrosis, nodular hyperplasia. Ascites. Confirmed at operation	11
194	Alcoholic. Recurrent ascites and oedema	25
195	Ascites. Also had nephritis. Cirrhosis confirmed <i>post mortem</i>	10
196	Alcoholic. Recurrent ascites and oedema. Liver enlarged, hard, and irregular	19
197	Banti's syndrome. Recurrent ascites. Splenomegaly	49
198	Alcoholic. Ascites. Epithelioma of palate	54
199	Hypertension. Ascites	60
200	Banti's syndrome. Cirrhosis confirmed <i>post mortem</i>	41
201	Very alcoholic. Enlarged liver and spleen	32
202	Diabetes and syphilitic aortitis. <i>Post mortem</i> , early biliary cirrhosis and a fibrotic gall-bladder	53
203	Diabetes. Alcoholic. Liver and spleen enlarged	63

TABLE VII  
*Cases of Hepatitis.*

Details of the cases of hepatitis with jaundice (Nos. 204 to 217) are given in Table IX of the Appendix. Although cases 218 and 219 had hepatitis, in both the cause of the jaundice was in doubt and they have not been included in Table IX.

Case No.	Remarks.	Choline esterase units.
218	Carcinoma of the pancreas, suppurative cholangitis, liver and pancreatic abscesses. Icterus index 110	23
219	Suppurating hydatid cysts of liver. Jaundice probably due to the impaction of a daughter cyst in the ampula of Vater. 10.9.38 Cholaemia. Icterus index 75 21.9.38 Dying. Icterus index 15	31 24
220	Liver abscesses, biliary fistula. Confirmed at operation	32
221	Multiple hydatid cysts of liver. Confirmed at operation	33
222	Amoebic abscess of liver. Confirmed at operation	30
223	Alcoholic hepatitis. Symptomatically well, but liver still enlarged	70
224	Solitary staphylococcal liver abscess. Confirmed at operation	49

TABLE VIII  
*Metastases in the Liver.*

Details of the cases of metastases in the liver with jaundice (Nos. 225 and 227 to 232) are given in Table IX of the Appendix. Case 226 is included in Table X.

Case No.	Remarks.	Choline esterase units.
233	Metastases from a carcinoma of the bronchus	31
234	Metastases from a carcinoma of the stomach	36
235	Ascites. Carcinoma of the stomach	30
236	Liver enormous (? carcinoma of the colon)	61
237	Metastases from a carcinoma of the bronchus	44
238	Metastases from a carcinoma of the stomach	37
239	Moribund (? carcinoma of the colon)	23
240	Metastases from a carcinoma of the bronchus	36
241	Metastases from a carcinoma of the stomach	38
242	Primary carcinoma unknown	44
243	Metastases from a carcinoma of the caecum	30
244	Primary carcinoma unknown	52
245	Metastases from a carcinoma of the stomach	52
246	? Carcinoma of the stomach	59

TABLE IX  
*Cases of Hepatic Jaundice.*

Case No.	Manner of diagnosis.	Duration of jaundice.	Remarks.	Choline esterase units.	Icterus index units.
146	Clin.	4 days	Heart failure. Mitral stenosis	17.6.37 1.7.37	40 30
			Improving	8.7.37	36
			Quite well	24.6.38	88
147	Aut.	1 wk.	Heart failure. Moderate	13.7.37	40
			Severe	30.7.37	26
					25 33 15 — 6 18

TABLE IX (continued)

Case No.	Manner of diagnosis.	Duration of jaundice.	Remarks.	Choline esterase units.	Icterus index units.
161	Aut.	5 days	Heart failure. Mitral stenosis	21	20
166	Aut.	4 days	Heart failure. Hypertension	22	15
178	Aut.	4 days	Prostatic uraemia	31	20
181	Aut.	4 days	Biliary cirrhosis, intrahepatic stones	34	25
182	Aut.	? 1 wk.	Subacute hepatic necrosis with multiple nodular hyperplasia. Jaundice previously	15	35
183	Clin.	6 wks.	Cirrhosis. Alcoholic. Enlarged, hard, and irregular liver	44	125
184	Clin.	3 days	Cirrhosis. Ascites 3 wks. Large hard liver	54	40
185	Clin.	?	Subacute hepatic necrosis with multiple nodular hyperplasia	20	45
186	Aut.	4 wks.	Subacute hepatic necrosis with multiple nodular hyperplasia. Jaundice previously	14	190
187	Oper.	4 mos.	Biliary cirrhosis. Large liver and spleen. Biopsy confirmation	25	115
188	Clin.	4 yrs.	Subacute hepatic necrosis with multiple nodular hyperplasia. Variable jaundice. Spleen palpable. Liver irregular 30.12.38	15	40
			Improved 20.3.39	26	25
189	Clin.	10 wks.	Subacute hepatic necrosis with multiple nodular hyperplasia. Jaundice 30 yrs. before. Spleen palpable. Liver irregular	31	55
190	Clin.	1 wk.	Subacute hepatic necrosis with multiple nodular hyperplasia. Spleen palpable, liver irregular. Telangiectasia	15	25
191	Clin.	4 mos.	Subacute hepatic necrosis with multiple nodular hyperplasia. Previous attack of jaundice 1 yr. before. Recovering	69	30
192	Aut.	? 3 wks.	Haemochromatosis. Primary liver carcinoma	30	170
204	Clin.	3 wks.	Toxic hepatitis. Deteriorating 19.3.37	20	140
			Worse. Ascites 23.3.37	20	—
			" 7.4.37	21	100
			Unchanged " 16.4.37	12	80
			Improving 5.5.37	15	40
			" 21.5.37	40	24
			Better 25.6.37	60	10
			Healthy 21.1.38	65	6
205	Clin.	3 days	Lobar pneumonia. Before crisis 5.10.37	27	17
			Crisis 8.10.37	22	8
			Recovered 10.11.37	54	7
206	Clin.	4 days	Incision of large abscess 10 days before. High fever until onset of jaundice 15.9.37	28	20
			Recovered 23.9.37	54	7
207	Clin.	3 wks.	Toxic hepatitis. Improving 3.8.38	25	200
			" 17.8.38	32	95
			" 26.8.38	31	45
			" 2.9.38	39	30
			" 12.9.38	43	25
			" 21.10.38	53	10
			Healthy 24.2.39	52	5
208	Aut.	2 days	Acute appendicitis. Toxic hepatitis	20	35
209	Aut.	3 wks.	Acute hepatic necrosis	39	275
210	Aut.	1 wk.	Carcinoma coli, pelvic abscess, hepatitis	10	30
211	Clin.	6 wks.	Atophan hepatitis. Transient diabetes. Recovering 19.10.38	36	40
			" 29.10.38	51	16
			Healthy 17.4.39	82	4

TABLE IX (continued)

Case No.	Manner of diagnosis.	Duration of jaundice.	Remarks.			Choline esterase units.	Icterus index units.
212	Clin.	3 days	Lobar pneumonia.	Before crisis	25.1.39	53	20
				After crisis	28.1.39	65	5
				Recovered	4.2.39	95	5
213	Aut.	4 days	Subacute bacterial endocarditis			39	15
214	Clin.	3 wks.	Arsenical hepatitis.	Improving	20.3.39	49	135
				"	23.3.39	50	130
				"	31.3.39	53	110
				"	12.4.39	65	42
215	Oper.	2 wks.	Right subphrenic abscess		24.4.39	35	12
			Unchanged		2.5.39	35	13
216	Clin.	1 day	Toxic hepatitis.	Onset	15.4.39	53	35
				Unchanged	17.4.39	51	30
				Improving	22.4.39	56	10
				Recovered	5.5.39	71	8
				Healthy	5.7.39	71	5
217	Clin.	6 days	Portal pyaemia.	Died; no post-mortem		36	45
225	Clin.	1 wk.	Liver metastases, ascites.	? Carc. coli		27	16
227	Aut.	4 days	Liver metastases.	Carc. coli	27.1.39	50	7
				" "	13.2.39	28	38
228	Oper.	5 wks.	Liver metastases.	? Carc. coli		30	210
229	Aut.	3 days	Liver metastases.	Carc. ventriculi		42	15
230	Aut.	2 wks.	Liver metastases.	Carc. bronchi		45	60
231	Clin.	14 wks.	Liver metastases.	Prim. not known		26	28
232	Oper.	2 wks.	Liver metastases.	Prim. not known		61	110

TABLE X

*Cases of Obstructive Jaundice.*

Case No.	Manner of diagnosis.	Duration of jaundice.	Remarks.			Choline esterase units.	Icterus index units.
226	Clin.	4 wks.	? Carcinoma of the head of the pancreas.			34	140
			Metastases in the liver				
247	Oper.	2 wks.	Stones in the common duct			71	36
248	Oper.	4 wks.	Chronic pancreatitis			71	85
249	Oper.	2 wks.	Stone in common duct			65	18
250	Oper.	4 wks.	Stone in common duct			54	95
251	Aut.	4 wks.	Carcinoma of papilla of Vater			55	50
252	Oper.	2 wks.	Stone in common duct			95	70
253	Aut.	5 wks.	Carcinoma of the head of the pancreas			51	100
254	Aut.	4 wks.	Carcinoma of papilla of Vater		15.12.37	75	65
					5.1.38 worse	41	100
					3.2.38 "	35	160
255	Clin.	4 days	Cholecystitis.	? Stone in common duct		59	42
256	Oper.	3 wks.	Gall-stones			54	60
257	Oper.	3 wks.	Carcinoma of the head of the pancreas			50	140
258	Oper.	2 wks.	Carcinoma of the head of the pancreas			68	45
259	Oper.	2 wks.	Stones in the common bile duct			77	30
260	Clin.	3 wks.	Gall-stones			87	60
261	Aut.	8 wks.	Carcinoma of the head of the pancreas			40	105

TABLE X (continued)

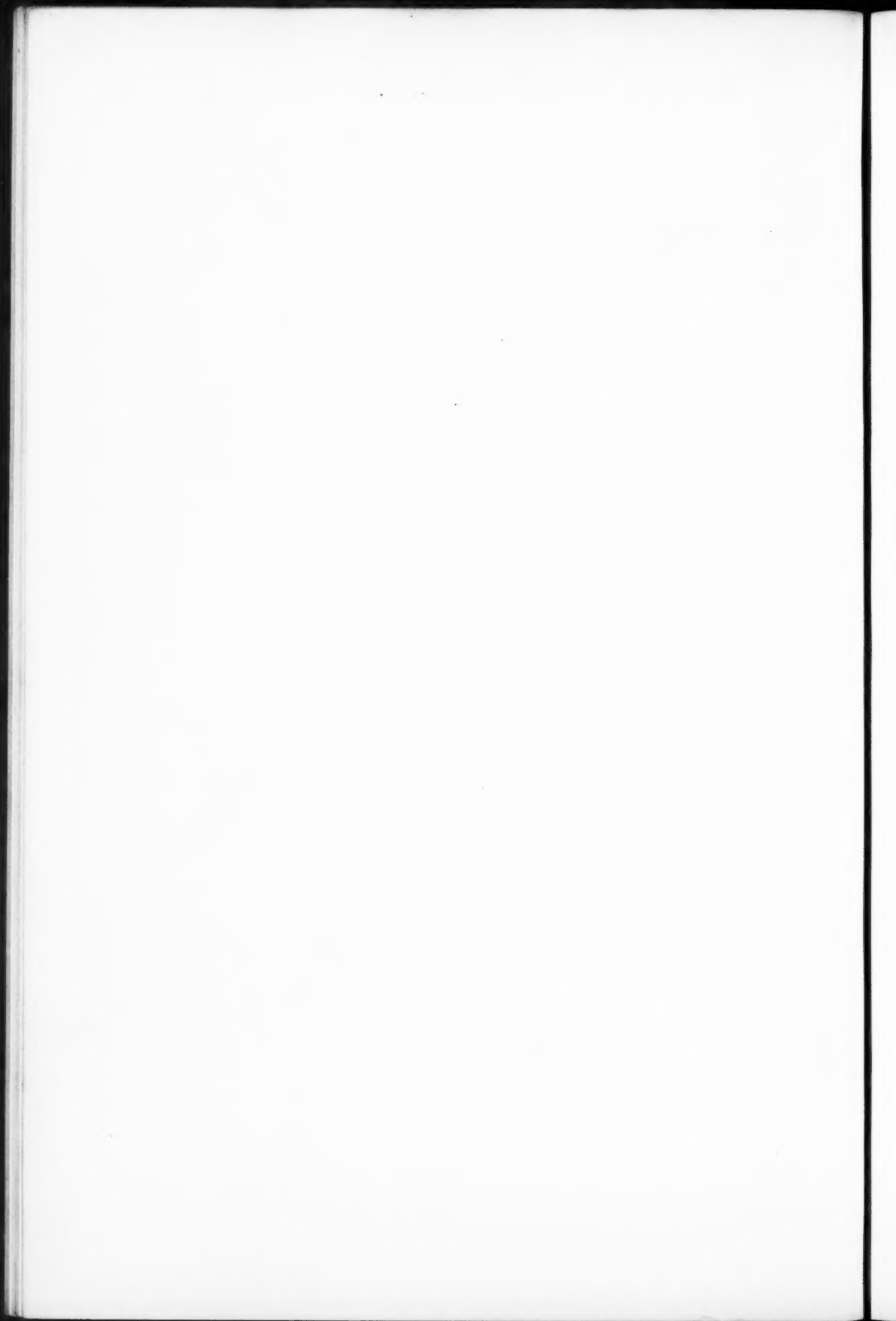
Case No.	Manner of diagnosis.	Duration of jaundice.	Remarks.	Choline esterase units.	Icterus index units.
262	Clin.	4 wks.	Carcinoma of the head of the pancreas	8.12.38 30.12.38	71 37
263	Clin.	1 day	Gall-stones		105 125
264	Clin.	1 wk.	Carcinoma of the head of the pancreas		69 25
265	Oper.	2 wks.	Gall-stones		58 110
266	Oper.	3 wks.	Stone in the common bile duct		47 65
267	Aut.	5 wks.	Carcinoma of the cystic duct	5.5.39	91 55
			No change	15.5.39	64 125
			No change	30.5.39	65 115
			Terminal streptococcal cholecystitis	13.6.39	67 130
268	Clin.	4 days	Stone in common duct		38 120
269	Oper.	3 wks.	Carcinoma of the head of the pancreas	16.6.39	75 13
			No change	4.7.39	52 210
			Cholecystenterostomy	5.7.39	41 210
			worse	12.7.39	32 240

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## NITROGEN AND CHLORIDE METABOLISM IN GASTRO-DUODENAL HAEMORRHAGE<sup>1</sup>

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### *Introduction*

THE discovery of a raised blood-urea in gastro-intestinal haemorrhage is comparatively recent; it was first reported by Sanguinetti in 1934. It had long been known that azotaemia might occur in the absence of organic renal disease in conditions such as intestinal obstruction (Tileston and Comfort, 1914), but the presence of such an 'extra-renal uraemia' in so common a condition as haematemesis awakened more general interest, especially in Denmark, where the work of Meulengracht (1934) on 'treatment with food' had already focused attention on gastro-intestinal bleeding.

It is not our intention to review the literature dealing with the azotaemia of haematemesis. Borst (1938) gives references to the papers which had appeared until that year, and many of these will be referred to in the subsequent discussion. Most of the published work has dealt with comparatively large series of cases, so that detailed investigation of individual patients has perforce been lacking. It was hoped that more intensive observations made on a small number of cases might clarify some aspects of the problem which a statistical approach had left obscure. This paper deals with our findings in three severe cases of gastro-duodenal haemorrhage.

### *Methods*

The patients were confined to bed throughout the period of the experiments. Except for the first patient, who was too ill, they were weighed daily on a recumbent personal weighing machine sensitive to changes of 25 gm. Twenty-four hour specimens of urine were collected in bottles containing toluene and 50 c.c. of glacial acetic acid. Specimens of faeces were transferred from the original vessels to porcelain pots containing acetic acid; later, after prolonged mechanical stirring, aliquot portions were taken for the various analyses.

The diet was planned to conform to the newer therapeutic principles of adequate food and fluid, and yet be simple enough to reduce analytical work to a minimum. Since we were studying especially the nitrogen balance, it

<sup>1</sup> Received September 30, 1939.

was necessary to keep the total nitrogen of the food down to a moderate though adequate level, so that any possible disturbance of balance would show more clearly from the data. At the same time it was necessary to avoid the risk of breakdown of body protein, arising merely from the diet being inadequate in protein content. The diet used provided 2,400 calories and 50 gm. of protein daily, and the total fluid intake was from four to five pints. The patient was fed hourly from 8 a.m. to 10 p.m.; eight of the feeds contained 45 gm. of Allenbury's diet in 5 oz. of water; the alternate feeds consisted of 1 oz. of glucose or lactose, according to taste, in 5 oz. of water. Each day the juice of one lemon and one orange was allowed for flavouring, and the patient was given water at night. This diet was taken well by two of the patients, but in the third case a milk, carbohydrate, and olive oil diet of the same calorie value and protein content had to be substituted on the third day of the period of observation; an aliquot portion of the day's supply of milk was taken for analysis.

Blood volume estimations were made, at first daily and later less frequently. At the same time, blood was collected in heparinized tubes under paraffin; the plasma was separated off within twenty minutes of the venepuncture.

The following technical methods were used:

- Blood.* Volume. Vital red method (Hooper, Smith, Belt, and Whipple, 1920).  
 Urea. Urease and nesslerization (Archer and Robb, 1925).  
 Total and non-protein nitrogen. Micro-Kjeldahl (Pregl, 1930).
- Plasma.* Chloride. Open Carius (Van Slyke and Sendroy, 1923).  
 Bicarbonate. Volumetric (Van Slyke, 1917).  
 Total base. Benzidine titration (Stadie and Ross, 1925).  
 Protein. Biuret colorimetric (Harrison, 1937).
- Urine.* Total nitrogen. Micro-Kjeldahl (Pregl, 1930).  
 Urea and ammonia. Urease and aeration (Van Slyke and Cullen, 1916).  
 Creatinine and creatine. Colorimetric (Folin, 1914).  
 Chloride. Volhard-Harvey titration (Harvey, 1910).  
 Uric acid. Colorimetric (Benedict and Franke, 1922).  
 Total base. Benzidine titration.  
 Inorganic phosphorus. Colorimetric (Berenblum and Chain, 1938).  
 Sulphur. Benzidine titration (Fiske, 1921).
- Faeces.* Chloride. Open Carius.  
 Nitrogen and sulphur. As for urine.  
 Iron. Case 1. Colorimetric (McCance, Widdowson, and Shackleton, 1936).  
 Cases 2 and 3. Titanous chloride titration (Klumpp, 1934).
- Food.* Chloride. (McCance, Widdowson, and Shackleton, 1936).  
 Nitrogen. Micro-Kjeldahl (Pregl, 1930).  
 Sulphur. As for urine.

*Case Reports*

*Case 1. Bleeding from gastric varices secondary to portal cirrhosis.* This man, aged 65 years, had an attack of haematemesis in February, 1938, from which he made a rapid recovery. On 12.11.38 a second haematemesis led to his admission to hospital. He continued to pass large melaena stools, and

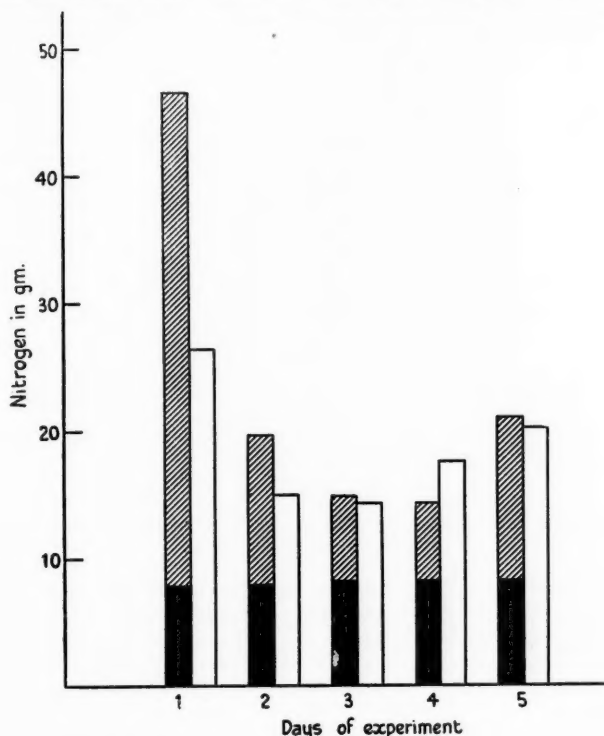


FIG. 1. Nitrogen balance in Case 1. The black portion of the left-hand column indicates nitrogen intake from food; the hatched portion intake from blood in the bowel; the right-hand column represents nitrogen output.

on 18.11.38 a further small haematemesis occurred. On admission, his blood-pressure was 200/90 and pulse-rate 100. Physical examination showed slight epigastric tenderness; the liver was not palpable. On 18.11.38 he was given a transfusion of 40 oz. of blood by the drip method. Although the blood volume and haemoglobin figures rose after transfusion, his general condition showed no corresponding improvement, and he died suddenly on 20.11.38. At the post-mortem examination, carried out by Dr. A. H. T. Robb-Smith, he was found to have a severe degree of cirrhosis of the liver. Bleeding had taken place from a ruptured gastric varix, and appears to have been persistent, as the stomach and intestines contained large amounts of blood-clot, some of which was recent. The heart showed acute interstitial myocarditis.

For the results of analyses see Tables I to VII<sup>2</sup> and Fig. 2.

*Case 2. Bleeding from chronic gastric ulcer.* Although our second patient, a

<sup>2</sup> Tables I-XXVII at end of article.

man of 57 years, had had three attacks of dyspepsia in the previous eighteen months, he felt perfectly well on the day of his haematemesis, and went to the cinema. A 5 p.m. on 23.3.39 he became suddenly faint, and vomited about a pint of blood. He was brought straight from the cinema to the hospital, and the blood-urea before 7 p.m. was 83 mg. per 100 c.c. He had

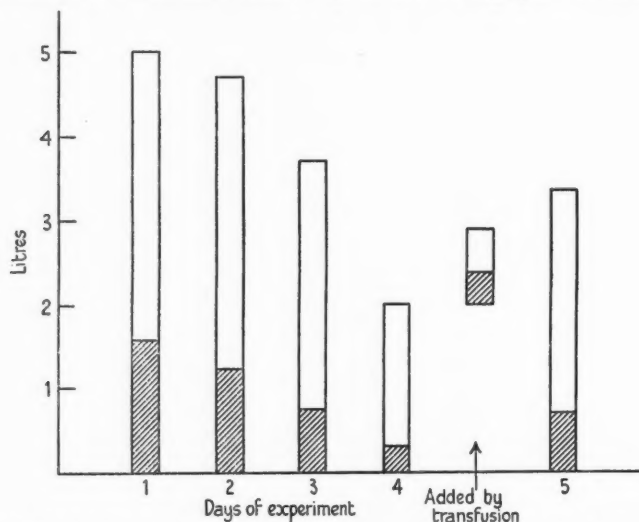


FIG. 2. Blood volumes in Case 1. The shaded portion represents cell volume, the unshaded plasma volume.

a blood-pressure of 94/60, and the heart-rate on auscultation was 160, completely irregular owing to auricular fibrillation. Physical examination showed some epigastric tenderness. On the next day he was much better, and he had no further vomiting. On 24.3.39 the bowels acted without an enema; on 28.3.39 a sharp attack of diarrhoea developed, and the collection of stools and urine had to be discontinued. Occult blood was absent from the faeces by 13.4.39. A barium meal on 14.4.39 showed a lesser curve gastric ulcer. He was sent to a convalescent home, and returned to the ward for a few days on 18.5.39. His haemoglobin then was 80 per cent. and he was feeling very well. His weight, which on admission was 51.05 kg., fell on the following day to 50.5 kg.; thereafter it did not change during the period of observation.

The results of analysis are shown in Tables VIII to XIII and in Fig. 3.

*Case 3. Bleeding from chronic duodenal ulcer* This man, who was 33 years of age, had had dyspepsia of duodenal ulcer type for about six years. In 1934 he had suffered from haematemesis. On 12.4.39 he was admitted to hospital after the passage of melaena stools for three days. Tenderness was present in the epigastrium, and the skin and mucosae were very pale. His haemoglobin at the time of admission was 45 per cent., but by the next day it had fallen to 26 per cent. His blood-pressure was 130/50. On 13.4.39 he had two small haematemeses; a drip transfusion of 50 oz. of blood was given from 4 p.m. to 10 p.m. His general condition improved very much after transfusion, and no further bleeding seems to have occurred. The bowels were opened by enema on 18.4.39 and on 21.4.39. A barium meal on



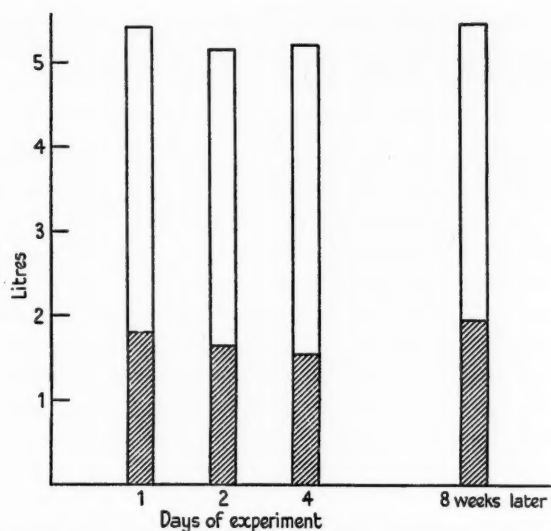


FIG. 3. Blood volumes in Case 2. The shaded portion represents cell volume, the unshaded plasma volume.

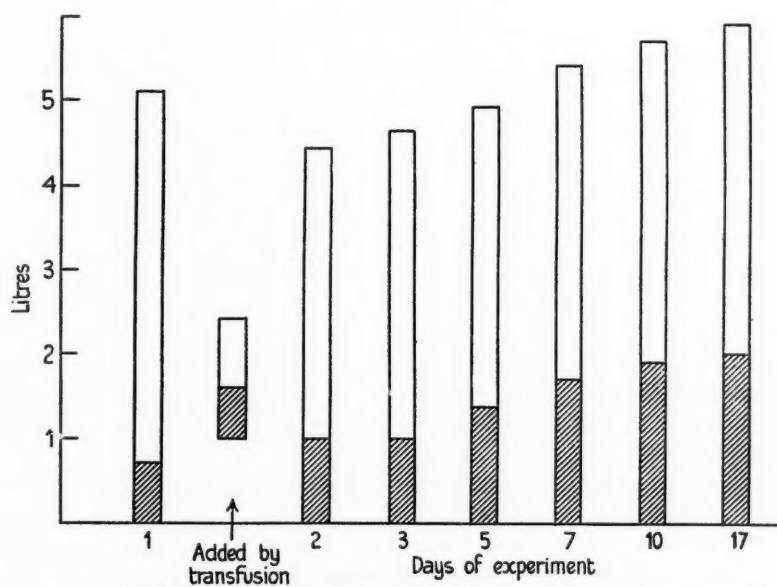


FIG. 4. Blood volumes in Case 3. The shaded portion represents cell volume, the unshaded plasma volume.

28.4.39 showed a posterior wall duodenal ulcer. Occult blood was absent from the stools on 26.4.39. On 13.5.39 he was sent to a convalescent home. Analyses are given in Tables XIV to XX and in Fig. 4.

### *Results*

Of the patients reported, the first had a severe and continued haemorrhage, which resulted ultimately in his death; the second man had a single haemorrhage of considerable severity; while the third made a recovery from a rather more protracted haemorrhage. The biochemical changes which we have observed in these different types of cases may now be considered.

1. *Azotaemia.* In none of these cases did the blood-urea attain the high levels which have previously been reported (e.g. 216 mg. per 100 c.c. by Alsted, 1936). The moderate degree of the azotaemia cannot be attributed to the haemorrhage being small, as one of the patients died, and all presented the appearance of severe shock, and passed large amounts of blood in the stools. Our patients, however, were given a free supply of fluid, and passed much larger amounts of urine in the twenty-four hours than cases of haematemesis not so treated; this maintenance of diuresis may well be responsible for the relatively low blood-urea values. The rise in non-protein nitrogen was similar in degree to the rise in blood-urea, and could be accounted for by the increase in urea nitrogen.

2. *The nitrogen balance.* It is difficult to determine the nitrogen balance in gastro-duodenal bleeding because of the loss by haematemesis or melaena of an unknown quantity of blood before the patient comes under observation, and the presence in the bowel of a quantity of blood, of which neither the volume nor the nitrogen content can be directly measured. In estimating the nitrogen intake, we have been obliged to make certain assumptions. The nitrogen content of the blood in the bowel has been assumed to be identical with that of a sample of venous blood on the day when bleeding occurred. For a measure of the quantity of blood lost into the bowel, we have relied on estimating the iron in the stool. Since the iron present in the shed blood in the bowel is almost entirely in the form of haemoglobin, it seems legitimate to suppose that very little will be absorbed. The iron content of the shed blood has been calculated from the haemoglobin content of a venous blood sample, the iron content of haemoglobin being taken as 0.34 gm. per cent. By dividing the iron found in the faeces by the iron content of 100 c.c. of the shed blood, the amount of blood lost has been estimated. The figures obtained are in harmony with the degree of anaemia. The nitrogen of this blood has been considered to form a portion of the nitrogen intake.

In the case of the first patient, who passed a daily stool, each stool was taken as belonging to the twenty-four-hour period immediately preceding. In the other two cases constipation was present; it has therefore seemed advisable to use metabolic periods of several days, each period ending with the passage of a stool. The daily blood sample involved a loss of 0.5 gm.

of nitrogen on the average. The blood given by transfusion in the first patient contained 16 gm. of nitrogen, and in the third patient 48 gm. It has been assumed that the blood administered by transfusion circulates unchanged, and does not represent a source of non-protein nitrogen. These amounts, therefore, are not included in the nitrogen balance, nor have we debited the patients with the nitrogen lost by haematemesis or melaena before they came under observation. Also, in Case 1, we have not taken account of the blood present in the bowel after death. The results in the first patient are given in Table XXI, and are also represented in Fig. 1. They show a retention of 25 gm. of nitrogen over a period of five days, the greater part of the retention occurring during the first two days of observation. It is noteworthy that this retention occurs in spite of a urinary nitrogen excretion averaging 12 gm. per diem, a finding which suggests that increased production or absorption, rather than faulty elimination, of non-protein nitrogen is responsible for the raised non-protein nitrogen of the blood. The blood in the bowel appears to be an important source of nitrogen; its estimated nitrogen content over the five-day period was 75.1 gm., while the faecal content of nitrogen over the same period was only 30.3 gm. This represents an absorption of 50 gm. of nitrogen from the shed blood, even if we allow only 1 gm. per diem for true faecal excretion of nitrogen.

In the second case, only one metabolic period of four days is available, owing to the onset of diarrhoea, which led to an abrupt diminution in the urinary output of nitrogen. The results, shown in Table XXII, indicate a retention of 9.9 gm. of nitrogen. Here, the estimated nitrogen content of the blood in the bowel is 26.8 gm., with a faecal content over the same period of only 4.1 gm.

The results obtained in the third case present certain difficulties of interpretation. Although there was no clinical evidence of bleeding after 15.4.39, the stool obtained by enema on 21.4.39 contained large amounts of iron. There is little doubt that this iron was derived from blood shed into the bowel during the period of active bleeding; a similar delay in the passage of blood has been noted by Hesser (1933). On this ground it appears necessary to consider the time from 13.4.39 to 21.4.39 as one metabolic period, since it is not possible to determine at what time or over how long a period the absorption of nitrogen from the shed blood actually took place. During this eight-day period there was a retention of 51.5 gm. of nitrogen. In the ensuing period of two days, at the end of which a stool was passed containing only a trace of iron, there was a negative nitrogen balance, output exceeding intake by 15.3 gm.

In all these cases, then, the period of bleeding was characterized by a positive nitrogen balance, although the output of nitrogen in the urine was normal or even increased. All the cases showed evidence of absorption of nitrogen from the bowel in considerable amount. In only one case was it possible to observe the period of recovery from the azotaemia; the nitrogen balance was then negative.

3. *The nitrogen partition in the urine* (Tables III, IV, X, XI, XVI, and XVII). The proportion of urinary nitrogen formed by urea nitrogen was 83 per cent. in the first patient, 81 per cent. in the third, and 84 per cent. in the second until the onset of diarrhoea led to an increase in ammonia output and a diminution in urea excretion. The average percentage of ammonia nitrogen was 2.7, 1.8, and 3.4 in the three cases. These values are within normal limits as given by Peters and Van Slyke (1931). Likewise, uric acid and creatinine excretion showed no striking changes. Creatinuria was not observed in the first two cases, but the urine of the third case showed an average of 0.18 gm. of creatine nitrogen per diem in the period from 13.5.39 to 18.5.39. During the same time the patient's weight fell from 67.7 kg. to 62.4 kg. After 18.5.39, the amount of creatine in the urine was within the limits of error of the method; the decline in the patient's weight was also arrested. The simultaneous occurrence of creatinuria and loss of weight suggests the presence of some breakdown of body protein, since there was no evidence of any dehydration to account for the loss of weight. Creatinuria has been observed in association with the muscle wasting of starvation (Benedict, 1915), and of hyperthyroidism (Palmer, Carson, and Sloan, 1929).

4. *Electrolytes in plasma and urine.* Borst (1936, 1938) has drawn attention to the association in gastro-intestinal bleeding of a high electrolyte content in blood and a low urinary electrolyte excretion; similar observations have been made by Allott (1939) in other morbid conditions. Only the first of our three patients showed this phenomenon; both plasma-chloride and total base were increased when the case came under observation; plasma bicarbonate and protein were at that time normal. In the next few days, the total base, chloride, and protein diminished steadily, the bicarbonate showing little change. The urinary output of total base averaged only 71 milli-equivalents per diem; this was associated with a low excretion of chloride, but the output of inorganic phosphorus and sulphur was normal. A possible explanation of the high plasma-electrolytes appears to be the passage of tissue fluid into the blood to make up plasma volume. Owing to the low content of protein, the base content of tissue fluid exceeds that of plasma by several milli-equivalents per litre (Peters and Van Slyke, 1931). Under normal circumstances the kidneys would rapidly excrete the excess of base, and restore the normal electrolyte concentration, described by Peters and Van Slyke as 'one of the most jealously guarded constants of the organism'. The cases reported by Borst and Allott were all critically ill. Blood volume estimations were not made on them, but in our patient who showed this phenomenon the blood volume was low. A deficient renal blood-flow impairs the efficiency of the kidney, both by diminishing glomerular filtration and by interfering with the nutrition of the tubule cells (Wood, 1936). In such circumstances the kidneys fail to make the optimum response. A somewhat similar state of affairs may be found in alkalosis, where the reaction of the urine is occasionally acid (Cooke, 1932), although the teleological indication is for the excretion of alkali.

In our second case, the total base remained the same during the initial period of observation, and on re-examination two months later the same value was found. The plasma-chloride, bicarbonate, and protein likewise showed no definite change. In Case 3, the initial total base level was the same as that observed one month after bleeding had ceased. In the days immediately after the bleeding, the total base showed a gradual decline, which was paralleled by the figures for chloride, bicarbonate showing little change. A similar gradual decline in total base was observed in the first case, after the initial period of high total base concentration. In Cases 2 and 3, the urinary output of total base was normal, averaging 141 and 160 milli-equivalents per diem.

The electrolyte changes in the plasma are thus somewhat variable, depending on the severity and duration of the bleeding. A short haemorrhage, even of considerable severity, may occur without any detectable alteration of the plasma-electrolytes. In cases of more protracted haemorrhage, where free entry into the blood of tissue fluid is combined with functional renal impairment, the plasma-electrolyte level may be increased, and that in the urine low. In the days succeeding haemorrhage, the plasma-electrolytes show a decrease to comparatively low levels.

5. *The chloride balance.* In working out the chloride content of the blood in the bowel, the same method has been followed as in the case of the nitrogen; the chloride absorbed from the blood in the bowel is included in the chloride intake, although chloride is free in the body, and not bound as in the case of nitrogen. No allowance was made for the chloride in sweat, as excessive sweating was absent in all cases.

The results in the first case are shown in Table XXIV. They indicate a considerable degree of chloride retention, mainly accounted for by very low urinary chlorides. Quite considerable amounts of chloride were present in the faeces; the continuous melaena from which this patient suffered may well account for the failure to absorb all the chloride from the shed blood. Although the chloride content of the food was not high, and no parenteral saline was given, this patient was found at autopsy to have widespread tissue oedema.

In Case 2 (Table XXV), there was a moderate degree of chloride retention, although the blood-chloride level was not altered.

In Case 3 (Table XXVI), chloride intake over the eight-day period from 13.4.39 to 21.4.39 exceeded output by 21.3 gm., although the plasma-chloride was low. The intake includes 23.3 gm. of chloride, the estimated content of the blood in the bowel; it is conceivable that part of this chloride is really referable to the period between the onset of bleeding and 13.4.39, when the patient first came under observation, and that the figures as given exaggerate the retention of chloride. Even if allowance is made for this possible error, a considerable retention of chloride must still have been present, as the chlorides of the urine and food are approximately equal over this period, and some chloride must have been absorbed from the blood in the bowel.



All three cases, then, showed a retention of chloride, although only one of them showed raised chlorides in the plasma.

6. *Sulphur metabolism.* The inorganic sulphur in urine was estimated in all three cases, and in Case 1, the sulphur in diet and faeces, and the urinary sulphur, were determined (Tables VII, XXVII). The output of sulphur in both urine and faeces showed a steady increase, while the N : S ratio in urine declined. These changes may indicate a different source of protein in the early and late part of the experimental period; haemoglobin has a low sulphur content, while tissue protein has a considerably higher content of sulphur.

7. *Blood volume* (Figs. 2, 3, 4). When the first patient came under observation, the total blood volume was 5 litres, but the red-cell volume already showed diminution. In the following three days, the cell volume and total blood-volume fell to very low levels. Transfusion on 18.11.38 produced only a partial restoration of blood volume. In the second patient, the blood volume did not change during the initial period of observation, and a control estimation made two months later was only slightly greater than that at the time of the bleeding.

Although the third patient showed great reduction of the red-cell volume at the first estimation, made before transfusion, the total blood volume was 5.1 litres. The first estimation after transfusion was actually lower, as regards total blood volume, but the cell volume was increased. The apparently anomalous decrease in plasma volume may be explicable in terms of the work of Robertson (1935) on bleeding in cats. He found that in two fatal bleedings, plasma volume was so much increased in consequence of a continual fall in blood-pressure that the blood volume was greater than before the haemorrhage; on the other hand, in animals which survived the haemorrhage, the increase in plasma volume was less pronounced. A decrease in plasma volume might thus occur as part of a general improvement in the patient's condition. In the succeeding days, both red-cell volume and total blood volume rapidly increased. The occurrence of substantial reduction in blood volume in gastro-intestinal bleeding has been demonstrated by Bennett, Dow, Lander, and Wright (1938); in 57 of their 122 cases more than 50 per cent. of the normal cell volume was lost.

#### *Discussion*

We may now attempt, in relation to the results given above, to put forward some explanation of the raised blood-urea in gastro-intestinal haemorrhage. In doing so, we must consider both the source of the urea and the causes which prevent its free elimination. There are two possible sources of urea—the protein of the blood in the bowel, and the protein of the tissues.

*Blood in the bowel.* Sanguinetti (1934) attached importance to the shed blood as a source of nitrogen; Ingegno (1935) and Alsted (1936) have also



put forward this view. Our own results demonstrate a considerable absorption of nitrogen from the bowel in all the cases. Meyler (1936) was able to raise the blood-urea from 40 to 60 mg. per 100 c.c. in a normal subject, by feeding with 1,500 c.c. of ox blood. The rise in blood-urea which can be attained by massive protein feeding is, however, a moderate one (Pepper and Austin, 1915), and it takes several hours to develop; it is thus inadequate to account for our observations in Case 2, where the blood-urea rose to 83 mg. per 100 c.c. within two hours of the haemorrhage. We consider that absorption of nitrogen from blood in the bowel is important in maintaining a moderately raised level of blood-urea for some time after the haemorrhage, but that it can scarcely account for the high values of blood-urea which have been recorded within a few hours of bleeding (Jones, 1939 *a*).

*Tissue protein.* In conditions such as external haemorrhage and intestinal obstruction, where there is no alternative source of nitrogen, breakdown of body protein must be of importance in causing azotaemia. Do our results afford any evidence of a similar occurrence in gastro-intestinal bleeding? We have previously described the patients as being in positive nitrogen balance, but this is a purely arbitrary conception which neglects the fact that a large part of their nitrogen intake is body protein (blood) that has been lost by bleeding. The patients begin the experiment with a debit of some 2.5 litres of blood or 75 gm. of nitrogen. A good deal of rearrangement and regeneration has to go on to make up for this, and it alone might account for the anomaly that the patients show creatinuria and loss of weight when they are in positive nitrogen balance, quite apart from the deleterious effect of haemorrhagic shock on the tissues.

In Case 1, we were unable to do daily weighing, and only traces of creatine were found in the urine. A progressive increase in the output of sulphur and of inorganic phosphorus was observed, a finding consistent with increased protein catabolism (Landauer, 1894).

In Case 2, the only change suggestive of protein breakdown was a loss in weight on the first day of 0.5 kg. In this case, however, the rise in blood-urea was very transient. If we assume that urea was equally diffused through the body fluids, which represent 70 per cent. of the patient's weight (Peters, 1935), a temporary rise of 50 mg. per 100 c.c. in the blood-urea could be produced by the breakdown of only 50 gm. of protein, an amount which might not lead to detectable creatinuria, or increase in phosphorus or sulphur excretion.

In Case 3, we found loss of weight, creatinuria, and a high output of inorganic phosphorus.

In each of these cases, then, we have found some evidence suggestive of protein breakdown. Little is known as to the cause of such a breakdown of protein. It does not appear to be associated with any increase of total metabolism; estimations of basal metabolism by the Roth-Benedict apparatus have been within normal limits in twelve of our cases of haematemesis. Christiansen (1935) has regarded the azotaemia as a symptom of intoxication

by the products of bacterial decomposition of the blood in the bowel; this explanation cannot apply to the early rise in blood-urea.

An increase in the non-protein nitrogen of the blood (Bang, 1916) and in nitrogen output (Straub, 1899) has been observed in states of dehydration. Spiegler (1901) attributes increased nitrogen output to cellular damage brought about by diminution in the fluids of the tissues. Although our cases were kept on an adequate intake of fluid, the loss of fluid by bleeding must have been made up to some extent by withdrawal of fluid from the tissues, and this disturbance of the *milieu interne* might possibly produce damage to the cells. Stewart and Rourke (1936) in external haemorrhage, and Borst (1938) in gastro-intestinal bleeding, have observed a substantial increase in the output of potassium in the urine; this suggests that intracellular fluid, which has a high potassium content, was drawn upon, as well as extracellular fluid. The extensive mobilization of intracellular fluid could scarcely occur without the possibility of protein breakdown.

Reference has already been made to the part which reduced blood volume may play in prolonging electrolyte disturbances in the plasma by interfering with kidney function. There is, too, the possibility that impaired blood supply to the tissues, which is known to produce local acidosis (Cannon, 1919), may also lead to destruction of protein. Increase in the non-protein nitrogen of the blood has been observed both in surgical shock (Aub and Wu, 1920), where the effective blood volume is diminished, and in wound haemorrhage (Duval and Grigaut, 1918).

Protein breakdown in our cases may therefore be attributed either to excessive withdrawal of tissue fluids, or to insufficient blood supply to the tissues, in consequence of reduction of circulating blood volume. It is perhaps worthy of mention that our third patient, the only one who showed creatinuria and considerable loss of weight, had treated himself by starvation for two days preceding admission to hospital. In cases treated by the older methods of food deprivation, the likelihood of a breakdown of protein due to actual wasting must have been great, and may have contributed to the high degree of azotaemia observed in them.

*Causes of deficient urea elimination.* It has already been mentioned that the rise in non-protein nitrogen after protein feeding is both slight and transient, and the increase in elimination required to maintain a normal blood-urea in these cases of haematemesis and melaena would be well within the range of a normal cardio-renal system. A measure of renal insufficiency must therefore be present throughout, and in a previous paper one of us has commented on the defective urea clearance (Black, 1939). We hope to discuss renal function in alimentary bleeding more fully in a subsequent paper; but whatever the mechanism of renal failure may be, the insufficiency is relative to increased urea production, and not absolute, since all our cases showed a normal output of nitrogen in the twenty-four hour urine.

*Conclusions*

Consideration of the evidence suggests that the initial rapid rise of blood-urea is due to a sudden increase in urea production, most probably from breakdown of tissue protein. In a case of moderate severity, when the patient has recovered from the initial shock of bleeding and gastro-duodenal distension, the kidneys are able to eliminate the excess of urea quite rapidly. In more severe cases, elevation of blood-urea persists, and is then due to absorption of nitrogen from the bowel, in conjunction with impairment of renal function, of which the most likely cause is diminished blood-flow to the kidneys.

Knowledge of the causes which lead to azotaemia in haematemesis appears to us to have an important bearing on the treatment of such cases. Our findings strongly support the advisability of early 'treatment with food' as advocated by Meulengracht (1935, 1936), and in this country by Witts (1937). The treatment with food should consist of a free intake of fluid, of salt, and of protein, in a diet of adequate calorie value. A free fluid intake produces diuresis, which favours the elimination of urea, it prevents extreme degrees of tissue dehydration, and it helps to maintain the blood volume within reasonable limits. Borst (1938) has advised against the giving of salt, on account of the hyperchloraemia which he observed. We found a raised plasma-chloride in only one of our cases, and even then it was a temporary phenomenon. The low output of chloride by the kidney in all our cases suggests that the body is faced with a deficiency of salt rather than an excess, so that the indication is for a free rather than a limited intake of salt, especially if vomiting is considerable in amount. An adequate amount of protein in the food is desirable, in spite of the presence in the bowel of large quantities of blood. The blood protein, while it serves as a source of urea, differs considerably in composition from the tissue proteins, and it is unlikely that it will act as a substitute for food protein in preventing wasting of the tissues. Equally important in the prevention of wasting is the provision in the diet of adequate calories, from 2,000 per diem in a patient of average size. Continued reduction of blood volume is deleterious both to kidney function and to the tissues generally and should be treated by blood transfusion; the indications for blood transfusion in haematemesis, and the technique to be employed, have been discussed by Jones (1939 *b*).

*Summary*

Biochemical investigations in three severe cases of gastro-duodenal haemorrhage are described. In addition to raised blood-urea and non-protein nitrogen, there were found:

- (1) A positive nitrogen balance, with evidence of absorption of nitrogen from the blood in the bowel.
- (2) A normal nitrogen partition in the urine, apart from the occurrence of creatinuria in one case.

(3) A tendency to diminution of the plasma-electrolytes as bleeding continued; the excretion of electrolytes in the urine was low in all three cases.

(4) A positive chloride balance.

(5) Decrease in total blood volume, with increase, relative or absolute, of the plasma volume.

The significance of the results is discussed, with special reference to the cause of raised blood-urea; and several therapeutic deductions are drawn.

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We are much indebted to Professor L. J. Witts for his constant interest and practical help in the conduct of the research, and in the preparation of this paper.

TABLE I

*Haematological Findings. Case 1*

Date.	Haemoglobin.		R.B.C. millions per c.mm.	W.B.C. per c.mm.	Mean corpuscular volume $\mu^3$ .	Mean corpuscular haemoglobin %.	Mean corpuscular haemoglobin %
	% Haldane.	gm. %					
Nov. 15	74	9.0	2.74	5,760	115	33	28.5
" 16	62	7.6	2.08	12,000	110	36.5	33
" 17	48	5.8	—	—	—	—	—
" 18	38	4.5	1.42	9,620	113	31.5	28
Transfusion							
" 19	50	6.0	2.14	12,000	99	28	28

TABLE II

*Blood and Plasma Analyses. Case 1*

Date.	Blood- urea mg. %	Blood N.P.N. mg. %	Plasma- protein gm. %	Plasma total base mEq. per l.	Plasma- chloride mEq. per l.	Plasma- bicarbonate mEq. per l.
Nov. 15	48	36	8.5	172	118	31.5
" 16	66	49	7.5	173	108	32
" 17	62	50	6.0	162	117	28.5
" 18	80	—	5.8	161	116	29
" 19	50	53	5.0	149	110	29

TABLE III

*Urine Nitrogen Output. Case 1*

Date.	Total N. gm. per diem.	Urea N. gm. per diem.	Ammonia N. gm. per diem.	Creatinine N. gm. per diem.	Creatine N. gm. per diem.	Uric acid N. gm. per diem.
Nov. 15	12.5	9.5	0.33	0.61	0.03	0.08
" 16	10.3	8.5	0.30	0.51	—	0.06
" 17	10.1	8.5	0.20	0.51	0.02	0.07
" 18	11.9	9.7	0.34	0.53	0.01	0.07
" 19	14.8	13.2	0.50	0.61	—	0.13

TABLE IV

*Urine Nitrogen Values (Percentages of Total Nitrogen). Case 1*

Date.	Urea N. %	Ammonia N. %	Creatine N and creatinine N. %	Uric acid N. %
Nov. 15-16	76	2.66	5.1	0.64
" 16-17	83	2.92	5.0	0.58
" 17-18	84	1.84	5.2	0.69
" 18-19	82	2.88	4.5	0.59
" 19-20	89	3.33	4.1	0.88

TABLE V

*Urine (Miscellaneous Values). Case 1*

Date.	Volume c.c.	Chloride mEq per diem.	Inorganic phosphorus gm. per diem.	Total base mEq per diem.
Nov. 15-16	840	42.5	0.7	78
" 16-17	690	27	0.68	48
" 17-18	780	35	0.68	69
" 18-19	1110	15	0.97	71
" 19-20	1750	13	1.57	90

TABLE VI

*Urinary Sulphur. Case 1*

Date.	Inorganic gm. per diem.	Ethereal gm. per diem.	Neutral gm. per diem.	Total gm. per diem.
Nov. 15-16	0.51	0.06	0.16	0.73
" 16-17	0.49	0.05	0.15	0.69
" 17-18	0.56	0.07	0.20	0.83
" 18-19	0.83	0.07	0.28	1.18
" 19-20	0.84	0.14	0.23	1.21

TABLE VII

*Analyses of Faeces and Vomit. Case 1*

	Nitrogen gm. per diem.	Iron mg. per diem.	Chloride gm. per diem.	Sulphur gm. per diem.
<i>Faeces</i>				
Nov. 15	13.32	534	6.65	0.36
" 16	3.83	134	1.20	0.12
" 17	3.69	75	1.25	0.14
" 18	4.55	59	0.19	0.14
" 19	5.03	173	0.25	0.29
" 20	4.06	74	0.08	0.11
<i>Vomit</i>				
Nov. 18	0.57	13	—	—

TABLE VIII

*Haematological Findings. Case 2*

Date.	Hb Haldane %	Hb gm. %	R.B.C. millions per c.mm.	W.B.C. per c.mm.	M.C. Vol. $\mu^3$ .	M.C. Hb $\gamma\gamma$ .	M.C. Hb %
Mar. 24	76	9.3	4.22	12,800	79	22	28
" 25	78	9.4	4.15	—	77	23	30
May 19	80	9.8	4.6	—	78	21	27

TABLE IX

*Blood and Plasma Analyses. Case 2*

Date.	Blood- urea mg. %	Blood N.P.N. mg. %	Plasma- protein gm. %	Plasma total base mEq per l.	Plasma- chloride mEq per l.	Plasma- bicarbonate mEq per l.
Mar. 23	83	—	—	—	—	—
" 24	90	56	6.0	148	105.5	23.6
" 25	40	—	6.75	—	102	31
" 26	54	31	6.0	146	106	34
" 27	43	31	—	147	105.5	28
" 29	44	29	—	147	104	28
May 19	34	—	7.5	147	103.6	29

TABLE X

*Urine Nitrogen Output. Case 2*

Date.	Total N gm. per diem.	Urea N gm. per diem.	Ammonia N gm. per diem.	Creatinine N gm. per diem.	Uric acid N gm. per diem.
Mar. 24-25	18.9	16	0.29	0.56	0.08
" 25-26	10.2	8.6	0.15	0.53	0.08
" 26-27	9.8	8.1	0.23	0.55	0.10
" 27-28	6.65	5	0.56	0.4	0.07
" 28-29	6.8	4.9	0.54	0.48	0.08

TABLE XI

*Urine Nitrogen Values (Percentages of Total Nitrogen). Case 2*

Date.	Urea %	Ammonia %	Creatinine %	Uric acid %
Mar. 24-25	84.5	1.5	3	0.4
" 25-26	85	1.5	5.2	0.8
" 26-27	83	2.35	5.6	1.0
" 27-28	75	8.4	6	1.1
" 28-29	72	8	7	1.2

TABLE XII

*Urine (Miscellaneous Values). Case 2*

Date.	Volume c.c. per diem.	Chloride gm. per diem.	Inorganic phosphates gm. per diem.	Inorganic sulphur gm. per diem.	Total base mEq per diem.
Mar. 24-25	1570	2.02	1.7	1.9	57
" 25-26	1500	2.36	0.57	1.6	174
" 26-27	1760	3.2	0.58	1.9	145
" 27-28	1175	2.16	0.48	1.4	108

TABLE XIII

*Analyses of Faeces. Case 2*

Date.	Nitrogen gm.	Chloride gm.	Iron mg.
Mar. 24	0.53	0.57	6.4
" 28	4.1	0.06	295



TABLE XIV

*Haematological Findings. Case 3*

Date.	Hb Haldane %	Hb gm. %	R.B.C. millions per c.mm.	W.B.C. per c.mm.	M.C. vol. $\mu^3$ .	M.C. Hb γγ.	M.C. Hb %
Apr. 13	27	3.1	1.47	26,000	88.5	21	24
" *14	52	6.2	2.61	22,400	86	24	28
" 15	52	6.2	2.60	8,500	86.5	24	28
" 17	—	—	2.87	8,000	—	—	—
" 19	60	7.2	3.43	—	93	21	23
" 22	74	9.0	4.0	—	83	25	30
" 29	80	9.8	4.5	—	78	22	28
May 12	86	10.5	4.4	—	82	24	29

\* Transfusion.

TABLE XV

*Blood and Plasma Analyses. Case 3*

Date.	Blood- urea mg. %	Blood N.P.N. mg. %	Plasma- protein gm. %	Plasma total base mEq per l.	Plasma- chloride mEq per l.	Plasma- bicarbonate mEq per l.
Apr. 13	62	52	5.2	159	100.6	26
" 14	54	—	5.75	152	99.5	32
" 15	44	22	5.5	151	95.9	27
" 17	50	29	6.5	153	93.5	30
" 19	43	36	—	144	93.5	31
" 22	35	31	7.5	—	94.7	32
May 12	40	26	—	160	100.5	29.5

TABLE XVI

*Urine Nitrogen Output. Case 3*

Date.	Total N. gm. per diem.	Urea N. gm. per diem.	Ammonia N. gm. per diem.	Creatinine N. gm. per diem.	Creatine N. gm. per diem.	Uric acid N. gm. per diem.
Apr. 13-14	23	18.8	0.74	0.78	0.10	0.12
" 14-15	21.8	18.3	0.38	0.84	0.22	0.11
" 15-16	16.4	12.7	0.58	0.64	0.17	0.14
" 16-17	16.4	13.7	0.68	0.67	0.27	0.17
" *17-18	10.1	8.7	0.45	0.4	0.09	0.07
	(16.4)	(14.1)	(0.73)	(0.65)	(0.15)	(0.11)
" 18-19	12.9	11.1	0.49	0.69	—	0.12
" 19-20	13.2	10.9	0.39	0.60	0.01	0.11
" *20-21	10.7	7.9	0.28	0.46	—	0.09
	(15.0)	(11.2)	(0.40)	(0.65)	—	(0.13)
" 21-22	12.8	11.1	0.43	0.65	0.05	0.16
" 22-23	19.7	13.7	0.78	0.62	0.01	0.13

\* On these two days the values for creatinine suggest that some urine was lost. The figures in brackets are values based on an assumed creatinine nitrogen output of 0.65 gm. per diem.

TABLE XVII

*Urine Nitrogen Values (Percentages of Total Nitrogen). Case 3*

Date.	Urea N. %	Ammonia N. %	Total creatinine N. %	Uric acid N. %
Apr. 13-14	82	3.2	3.8	0.5
" 14-15	84	1.75	4.9	0.5
" 15-16	77.5	3.5	4.9	0.9
" 16-17	83.5	4.1	5.7	1.0
" 17-18	85	4.45	4.9	0.7
" 18-19	86	3.8	5.4	0.9
" 19-20	82.5	3.0	4.7	0.8
" 20-21	74	2.6	4.3	0.9
" 21-22	86.5	3.4	5.5	1.2
" 22-23	70	4.0	3.2	0.7

TABLE XVIII

*Urine (Miscellaneous Values). Case 3*

Date.	Volume per c.c. diem.	Chloride gm. per diem.	Inorganic phosphorus gm. per diem.	Inorganic sulphur gm. per diem.	Total base mEq per diem.
Apr. 13-14	1650	1.06	1.55	2.3	164
" 14-15	1990	4.15	2.52	2.2	196
" 15-16	2440	4.53	1.66	2.3	128
" 16-17	2600	2.76	1.26	0.7	171
" *17-18	1570 (2550)	1.02 (1.66)	(1.16)	0.6	78 (127)
" 18-19	2130	0.70	1.28	0.8	161
" 19-20	1760	0.78	2.0	0.8	127
" *20-21	1200 (1700)	0.48 (0.68)	1.25 (1.77)	0.8 (0.8)	98 (138)
" 21-22	2070	0.95	1.12	0.7	140
" 22-23	2280	1.5	1.56	0.7	148

\* Figures in brackets are values corrected on the assumption of a creatinine nitrogen output of 0.65 gm. per day.

TABLE XIX

*Analyses of Faeces and Vomit. Case 3*

Date.	Nitrogen gm.	Chloride gm.	Iron mg.
<i>Faeces</i>			
Apr. 18	3.72	0.28	836
" 21	4.9	0.16	1018
" 23	1.4	0.18	8
<i>Vomit</i>			
Apr. 13	0.31	0.21	—

TABLE XX

*Weights. Case 3*

Date.	Weight kg.
Apr. 13	67.7
" 14	66.1
" 15	65.9
" 17	63.5
" 18	62.4
" 19	61.8
" 20	61.6
" 21	61.7
" 22	61.3

TABLE XXI

*Nitrogen Balance. Case 1*

Date.	Intake.			Output.			
	Food gm.	Blood in bowel gm.	Total gm.	Urine gm.	Faeces gm.	Vomit gm.	Total gm.
Nov. 15-16	7.9	38.5	46.4	12.5	13.3	—	25.8
" 16-17	8.0	11.5	19.5	10.3	3.8	—	14.1
" 17-18	8.2	6.4	14.6	10.1	3.7	—	13.8
" 18-19	8.2	6.1	14.3	11.9	4.5	0.6	17.0
" 19-20	8.2	12.6	20.8	14.8	5.0	—	19.8
5 days	40.5	75.1	115.6	59.6	30.3	0.6	90.5

TABLE XXII

*Nitrogen Balance. Case 2*

Date.	Intake.			Output.		
	Food gm.	Blood in bowel gm.	Total gm.	Urine gm.	Faeces gm.	Total gm.
Mar. 24-25	8.2	—	—	18.9	—	—
" 25-26	8.2	—	—	10.2	—	—
" 26-27	8.2	—	—	9.8	—	—
" 27-28	8.2	26.8	—	6.7	4.1	—
4 days	32.8	26.8	59.6	45.6	4.1	49.7

TABLE XXIII

*Nitrogen Balance. Case 3*

Date.	Intake.			Output.			
	Food gm.	Blood in bowel gm.	Total gm.	Urine gm.	Faeces gm.	Vomit gm.	Total gm.
Apr. 13-14	4.1	—	—	23	—	0.3	—
" 14-15	6.2	—	—	21.8	—	—	—
" 15-16	8.2	—	—	16.4	—	—	—
" 16-17	8.8	—	—	16.4	—	—	—
" 17-18	8.8	60	—	16.4	3.7	—	—
5 days	36.1	60	96.1	94.0	3.7	0.3	98
Apr. 18-19	8.8	—	—	12.9	—	—	—
" 19-20	8.8	—	—	13.2	—	—	—
" 20-21	8.8	73	—	15.0	4.9	—	—
3 days	26.4	73	99.4	41.1	4.9	—	46
Apr. 21-22	8.8	—	—	12.8	—	—	—
" 22-23	8.8	1	—	19.7	1.4	—	—
2 days	17.6	1	18.6	32.5	1.4	—	33.9

*Note to Tables XXI-XXIII.* In the first and third cases, it is possible that part of the nitrogen intake credited to blood in the bowel may have been absorbed and even excreted before the metabolic observations commenced. In the second case, this possibility can be definitely excluded (see reports of cases for dates).

TABLE XXIV  
Chloride Balance. Case 1

Date.	Intake.			Output.		
	Food gm.	Blood in bowel gm.	Total gm.	Urine gm.	Faeces gm.	Total gm.
Nov. 15-16	6	6.5	12.5	1.5	6.4	8.2
" 16-17	3	1.8	4.8	1.0	1.2	2.2
" 17-18	3	1.3	4.3	1.2	1.2	2.4
" 18-19	3	1.5	4.5	0.5	0.2	0.7
" 19-20	3	3.3	6.3	0.5	0.3	0.8
5 days	18	14.4	32.4	4.7	9.6	14.3

TABLE XXV  
Chloride Balance. Case 2

Date.	Intake.			Output.		
	Food gm.	Blood in bowel gm.	Total gm.	Urine gm.	Faeces gm.	Total gm.
Mar. 24-25	3	—	—	2.0	—	—
" 25-26	3	—	—	2.4	—	—
" 26-27	3	—	—	3.2	—	—
" 27-28	3	2.9	—	2.2	0.6	—
4 days	12	2.9	14.9	9.8	0.6	10.4

TABLE XXVI  
Chloride Balance. Case 3

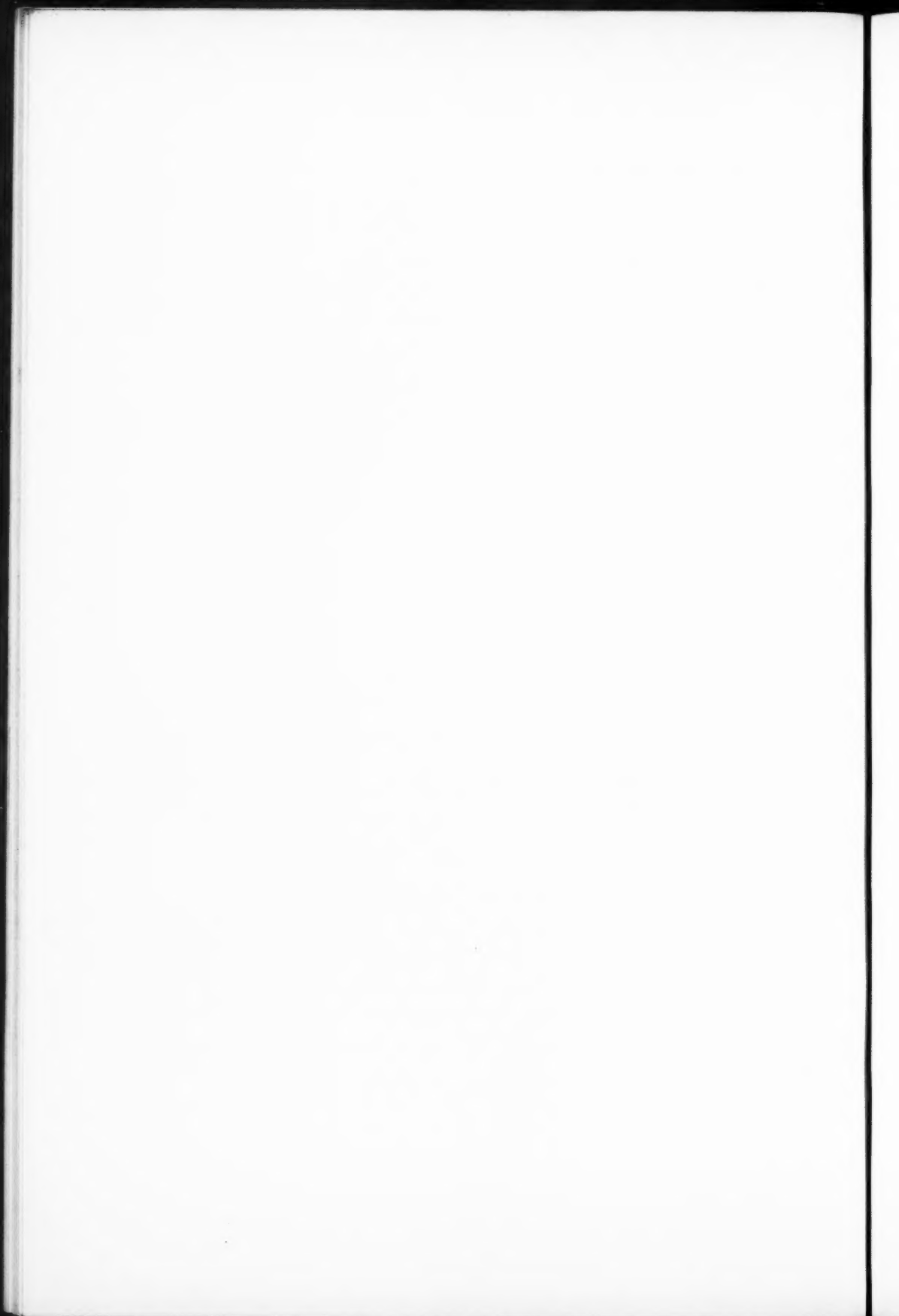
Date.	Intake.			Output.		
	Food gm.	Blood in bowel gm.	Total gm.	Urine gm.	Faeces gm.	Total gm.
Apr. 13-14	1.5	—	—	1.1	—	—
" 14-15	2.3	—	—	4.0	—	—
" 15-16	3.0	—	—	4.5	—	—
" 16-17	1.6	—	—	2.8	—	—
" 17-18	1.6	10.5	—	1.7	0.3	—
" 18-19	1.6	—	—	0.7	—	—
" 19-20	1.6	—	—	0.8	—	—
" 20-21	1.6	12.8	—	0.7	0.2	—
8 days	14.8	23.3	38.1	16.3	0.5	16.8
Apr. 21-22	1.6	—	—	1.0	—	—
" 22-23	1.6	—	—	1.5	0.2	—
2 days	3.2	—	3.2	2.5	0.2	2.7

TABLE XXVII  
Sulphur Balance. Case 3

Date.	Intake.	Output.			N : S ratio in urine.
	Food gm.	Faeces gm.	Urine gm.	Total gm.	
Nov. 15-16	0.53	0.36	0.73	1.09	17.1
„ 16-17	0.54	0.12	0.7	0.82	14.6
„ 17-18	0.56	0.14	0.83	0.97	12.2
„ 18-19	0.56	0.14	1.18	1.32	10.1
„ 19-20	0.56	0.29	1.21	1.50	12.2
5 days	2.75	1.05	4.65	5.7	—

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## GALACTOSE TOLERANCE AS A TEST OF LIVER FUNCTION<sup>1</sup>

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### *Introduction*

THE term 'liver function test' has been applied to such a large number of procedures, some having no very certain relationship to the liver, that it is desirable to consider briefly the general principles underlying these tests. The most useful classification appears to be the following:

(A) *Tests Depending upon the Excretion of Bile:*

Van den Bergh reaction, icterus index.  
Bromsulphalein excretion test.  
Serum phosphatase and cholesterol estimations.  
Examination of duodenal fluid.  
Cholecystography.

(B) *Tests not Depending on the Excretion of Bile:*

Deaminating function (*estimation of blood amino-acids*).  
Detoxicating function (*hippuric acid and salicyluric acid tests*).  
Glycogenic function (*glucose, laevulose, and galactose tolerance tests*).

Numerous other proposed tests appear to have been abandoned by most workers, and even in this restricted list, those in italics are not usually considered to be of any clinical value for the present purpose. The virtue of this division into two classes becomes obvious when we consider the problem of distinguishing jaundice due to obstruction of the bile passages from jaundice due to intrahepatic disease, e.g. toxic hepatitis or cirrhosis of the liver. The excretion of bile is obviously interfered with in both groups, and it is reasonable that the distinction should be made most easily by testing a function which is independent of excretion. Moreover, in this second group it often happens that the excretory function is affected much less than other functions. In support of this statement, it is only necessary to recall the frequency with which advanced hepatic cirrhosis is associated with slight or absent jaundice. It is thus, particularly in the case of generalized lesions of the liver parenchyma, that liver function tests of type 'B' are indicated. This term is intended to include such conditions as toxic hepatitis, focal hepatic necrosis, acute yellow atrophy, cirrhosis of the liver, and ascending cholangitis. We may note here that some kind of generalized liver damage is now recognized in an increasing range of diseases,

<sup>1</sup> Received October 9, 1939.

some recent additions being hyperthyroidism (Beaver and Pemberton, 1933), pneumonia (Curphey and Solomon, 1938), rheumatoid arthritis (Rawls, Weiss, and Collins, 1937), and following certain surgical operations (Boyce and McFettridge, 1938). For the sake of completeness we may list here the commoner of the better known causes, which are catarrhal jaundice, chemical poisoning, certain spirochaetal diseases, toxæmia of pregnancy, and chronic alcoholism.

The present paper is concerned with the galactose tolerance test, which depends upon the fact that galactose is removed from the blood-stream chiefly by the liver, being converted presumably to glycogen (Mann, 1934). It is also utilized slightly by other tissues (Bollman, Mann, and Power, 1935), but to a much smaller extent than glucose or laevulose. In this connexion Mann's opinion of the relative suitability of galactose and laevulose as test agents is of interest in view of a number of recent papers on the laevulose tolerance test (Stewart, Scarborough, and Davidson, 1938, Herbert and Davison, 1938). Mann wrote in 1934: 'Although the liver does make glycogen from laevulose, the muscles can do this also and laevulose can be utilized by an animal without a liver. Consequently, it is difficult to understand how a laevulose tolerance test could be used to measure hepatic injury. Theoretically, it should be possible to indicate hepatic injury by a galactose tolerance test, as the utilization of this sugar appears to depend chiefly on the liver.' If we add to this the fact that blood-galactose is much easier to estimate than blood-laevulose, the advantage of the former sugar appears to be indisputable. The only minor drawback is the somewhat greater cost of the test dose of galactose, about 2s. 8d. as opposed to 1s. 1d.

The galactose test has in the past been used in various ways:

- (1) Oral galactose: blood-sugar determined (Beaumont and Dodds, 1931).
- (2) Oral galactose; urine sugar (or galactose) determined (Shay and Fieman, 1937).
- (3) Intravenous galactose; blood-galactose determined (King, 1938).
- (4) Oral galactose; blood-galactose determined (Althausen and Wever, 1937).

Of these possibilities, the first has the obvious disadvantage of failing to allow for variations in blood-glucose. A considerable rise of blood-glucose often occurs after oral galactose in normal persons (Harrison, 1938), and this rise is of course accentuated in diabetes (see Fig. 3). This modification has in consequence been largely discarded, except by Uexkull (1939). Similar considerations apply to the second method, unless the urinary glucose is removed by yeast fermentation. This has been advocated by Shay and Fieman (1937) who gave 40 gm. of galactose by mouth and then collected the urine up to five hours. Not more than 3 gm. of galactose should be excreted in this time, so that yeast fermentation was performed if the total sugar exceeded this amount. These authors found the test valuable if performed early in differentiating toxic from obstructive jaundice. Robertson, Swalm, and Konzelmann (1932), on the other hand, state that it gives too

many negative results. In my experience the urinary galactose excretion has depended too much on the rate of urinary flow to be a reliable guide. For example, investigation of one patient suffering from Graves' disease gave the following results:

Blood galactose at $\frac{1}{2}$ , 1, $1\frac{1}{2}$ , 2 hrs. in mg. %	Urinary volume in 2 hrs. in c.c.	Urine-galactose in gm.
81 128 78 5	250	4.0
47 149 98 39	28	0.9

It will be noticed that on the second occasion, although the blood-galactose values were higher, the urinary output was less than one quarter of that on the first occasion, a finding which is presumably to be correlated with the smaller urine volume. The third method has been used by King (1938), but his results have not yet been published. The present paper is concerned with the development of the fourth possibility, which appears to be the method of choice. It presents two advantages over the third method. Firstly, greater convenience, for the technique of preparing and injecting 50 c.c. of galactose solution intravenously is somewhat laborious, and unpleasant for the patient. Secondly, the galactose is presented to the liver by the physiological route, the portal vein. It may well be that there is a difference in the power of the liver to deal with galactose arriving by this route rather than from the general circulation, and furthermore in this method the sugar reaches the liver before it reaches the other organs. On the other hand, the question of varying rates of absorption from the alimentary tract requires to be considered, but the results given below show that such variations do not in fact destroy the value of the test, except, of course, when obvious failure of absorption is present, e.g. pyloric stenosis, post-anaesthetic state. Very few observations by this method appear to have been made, which is remarkable when it is realized that the principles of blood-galactose determination were fully established by Raymond and Blanco in 1928. The only clinical paper which I have found is that of Althausen and Wever (1937) describing the determination of the blood-galactose after an oral dose of 40 gm. at intervals of five, fifteen, and thirty minutes. Twenty-one normal persons were tested, and normal curves were also obtained in 14 cases of diabetes mellitus. An impairment of liver function was noted in Graves' disease. No cases of jaundice or hepatic cirrhosis were tested. As will appear later, the blood-galactose may not reach its maximum after this dose until 1 or  $1\frac{1}{2}$  hours after administration, so that it is desirable to extend the time of the test well beyond thirty minutes.

#### *Methods*

The patient is starved overnight, no breakfast or morning tea being allowed. A dose of 40 gm. of galactose, dissolved in 250 c.c. of water, is given by mouth. It is necessary to use hot water and cool subsequently, to obtain complete solution. Blood is then collected into a fluoride or oxalate tube at  $\frac{1}{2}$ , 1,  $1\frac{1}{2}$ , and 2 hours after the solution has been drunk.

Either venous or capillary blood may be used. In the latter case it is convenient to collect 0.3 to 0.4 c.c. from the ear into a small tube  $1'' \times \frac{1}{4}''$ , the sides of which are coated with a mixture of potassium oxalate and sodium fluoride. The use of the sterile glass pricker described by Harrison (1938) is of great assistance here, making possible in most cases the collection of all the samples from a single ear puncture.

The following blood-galactose method is based on that of Harding, Grant, and Glaister (1933), for the details of which I am indebted to Dr. E. J. King, and also upon the method of Raymond and Blanco (1928). The sugar reagent is a modification of Somogyi's reagent No. 2 (Peters and Van Slyke, 1932). The method depends upon the preliminary removal of glucose from the blood by yeast fermentation, followed by deproteinization and determination of the copper-reducing power. The modifications introduced include the new sugar reagent and the use of a weaker (0.002 N.) thiosulphate solution, which result in increased accuracy.

*Solutions.* (1) Alkaline-copper-iodine reagent. Dissolve 25 gm. of anhydrous sodium carbonate, 20 gm. of sodium bicarbonate, and 25 gm. of Rochelle salt (sodium potassium tartrate) in 600 c.c. of water. Dissolve 7.5 gm. of copper sulphate ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) separately in about 100 c.c. of water. Introduce the copper solution into the carbonate-tartrate solution through the funnel, the tip of which rests on the bottom of the beaker, stirring the solution well during the addition to prevent loss of carbon dioxide. Add to the mixture 5 gm. of potassium iodide and 0.175 gm. of potassium iodate ( $\text{KIO}_3$ ). Dilute to 1 litre.

(2) Isotonic sodium sulphate (3 per cent.).

(3) 10 per cent. sodium tungstate.

(4) 7 per cent. copper sulphate.

(5) N/1 sulphuric acid.

(6) 0.002 N. sodium thiosulphate. This must be freshly prepared each day by accurately diluting N/10 sodium thiosulphate 50 times.

(7) 1 per cent. starch solution in saturated sodium chloride.

*Yeast tubes.* Place 1 c.c. of a 1 in 3 suspension in water of fresh brewers' or bakers' yeast into a 15 c.c. round-bottomed centrifuge tube,  $4\frac{3}{4}'' \times \frac{5}{8}''$ , add 10 c.c. of distilled water, mix thoroughly with a glass rod, and centrifuge for about five minutes at 3,000 revolutions per minute. Decant the supernatant liquid and repeat the washing twice with 10 c.c. of water. At the end of the last washing, drain the tube for a few minutes on a filter paper, and wipe the inside thoroughly with strips of filter paper. Finally, add 2.2 c.c. of isotonic sodium sulphate.

*Determination.* Place 0.2 c.c. of blood into a yeast tube; mix thoroughly with a glass-rod and allow to stand for fifteen minutes at room temperature. A blank should be put up at the same time, using 0.2 c.c. of blood containing no galactose. This blood may be any sample, preferably fairly normal in character, undergoing routine analysis. This blank tube controls the completeness of removal of glucose, and should give a titration almost identical

with the reagent blank (2 c.c. of water plus 2 c.c. of sugar reagent) which is done occasionally as a check on the thiosulphate solution. It is also desirable to include one further tube containing 2.0 c.c. of isotonic sodium sulphate, 0.2 c.c. of galactose-free blood, and 0.2 c.c. of 0.1 per cent. galactose solution. The occasional samples of yeast which attack galactose are detected by this tube. In my experience only two such yeasts were found out of about one

TABLE I

Blood galactose mg. per 100 c.c.	c.c. of 0.02 N thiosulphate (blank minus unknown).
0	0
20	0.13
60	0.89
130	2.14
180	3.08
240	4.42

hundred tested.<sup>2</sup> At the end of fifteen minutes add 0.3 c.c. of 10 per cent. sodium tungstate, mix thoroughly by shaking, then add 0.3 c.c. of 7 per cent. copper sulphate and mix again. It is essential to mix before adding the copper sulphate solution, otherwise incomplete protein precipitation results. Centrifuge for about five minutes, and decant the supernatant fluid into a pointed centrifuge tube. Pipette 2 c.c. of the centrifugate into a 5" ×  $\frac{3}{4}$ " test tube, followed by 2 c.c. of the alkaline copper iodine reagent, which must be added by means of an accurate, Grade A, grease-free pipette, which should be kept in dichromate-sulphuric acid cleansing mixture when not in use; traces of grease render it impossible to measure exactly 2 c.c. of this reagent. Mix by shaking, and cover the top of the tube with a large glass marble, or else plug loosely with cotton wool. Place the tubes in a briskly boiling water bath for *exactly* ten minutes, cool in running water for two minutes, and immediately add 2 c.c. of normal sulphuric acid and shake once. Keep the tube covered and titrate as soon as possible with 0.002 N. sodium thiosulphate, using a 5 c.c. microburette and adding finally 1 drop of starch solution as indicator. The blank requires 4.8 to 4.9 c.c. of thio-sulphate. The difference between the blank and the unknown titre is the figure used in calculating the blood-galactose. It is necessary to arrange that the heating, cooling, and titration are all done consecutively and without delay, although the tubes may be left if necessary for some hours before heating. This is because either re-oxidation of cuprous oxide or evaporation of iodine will otherwise cause errors. The former error is more serious than the latter, hence the direction to add the sulphuric acid immediately after cooling. The iodine liberated then oxidizes all the cuprous oxide.

*Calculation.* Since the relationship between the thiosulphate titre and the blood-galactose is not quite capable of representation by a straight line it is necessary to prepare a calibration curve. This is made by putting up a series of yeast tubes containing 2.0 c.c. of isotonic sodium sulphate and 0.2 c.c. of galactose-free blood (preferable from a normal or nearly normal

<sup>2</sup> A yeast which has been proved suitable may be stored for at least one month in a stoppered vessel in the refrigerator.

person). Samples of 0.2 c.c. of galactose solutions of known strengths are then added to the tubes, each strength being represented in duplicate, and the estimation completed as above. The figures in Table I were obtained in this way and may be used to construct a curve, but it is preferable for each laboratory to have its own calibration data.

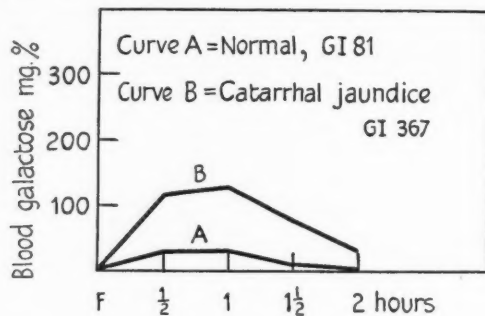


FIG. 1.

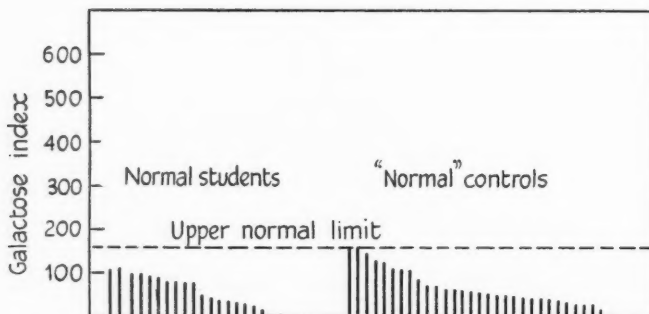


FIG. 2.

### Results

Fig. 1 shows a typical normal and a typical abnormal curve. The maximum blood-galactose may occur at  $\frac{1}{2}$ , 1, or  $1\frac{1}{2}$  hours (usually 1 hour), and the sum of these four values, for which the term 'galactose index' (G.I.) is suggested, appears to be the best criterion to take for purposes of comparison, and tends to be about double the highest value. Fig. 2 and Appendix I give the results of the test on 50 normal persons, of whom 20 were healthy male medical students, and 30 were patients from the out-patient department suffering from various diseases unconnected with the liver, thyroid, or gastrointestinal tract. There is usually a fairly close correlation between the galactose index and the highest value, and it is evident that a peak value of 80 mg. of galactose per 100 c.c. or a G.I. of about 160 may be taken as the upper normal limit. The average normal G.I. is 68. It is noticeable that the students gave a slightly lower reading than the 'normal' controls, who provide eight cases with a G.I. between 100 and 160 as opposed to



only two students in this range. However, the difference is hardly great enough to be of clinical importance.

Fig. 3 gives the results obtained in diabetes mellitus (six cases), toxic jaundice (10 cases), obstructive jaundice (six cases), and Graves' disease (12 cases). The normal figures in diabetes mellitus are in confirmation of

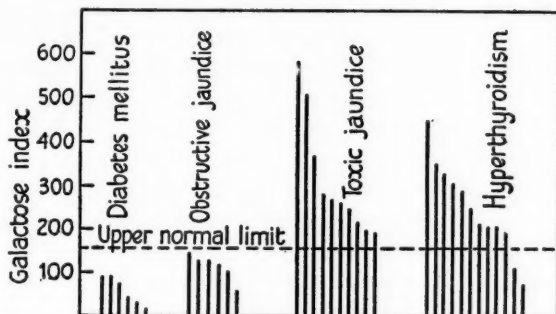


FIG. 3.

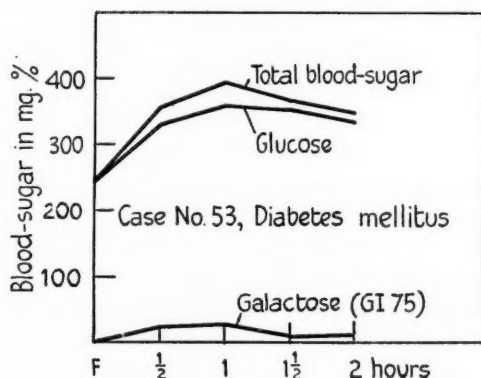


FIG. 4.

those which Althausen and Wever (1937) obtained with the half-hour galactose test. The dissociation between the blood-glucose and blood-galactose in diabetes is well shown in Fig. 4. It will be seen that the 16 cases of jaundice were satisfactorily differentiated, for all the toxic and none of the obstructive cases showed impairment of liver function. This suggests that the test should be of some value in the differential diagnosis of jaundice. In 10 out of 12 cases of Graves' disease definite impairment of function was seen, in some cases of extreme degree. These were clinically severe cases, with basal metabolic rates ranging from +20 to +80 per cent. (average +55 per cent.). This finding is in agreement with the results of Boyce and McFettridge (1938), who used the hippuric acid test. There seems little doubt that this liver damage is a part of the pathology of hyperthyroidism, although it has not yet received general recognition. Support for this view from the morbid

anatomist's standpoint will be found in a paper by Beaver and Pemberton (1933). This subject has been pursued in collaboration with Mr. Frank Rundle, and a paper is in course of preparation.

### *Discussion*

The value of any liver function test must depend upon three things; firstly its sensitivity, secondly the nature of the function tested, and thirdly on the intelligent clinical use of what is, in effect, simply an additional physical sign. With regard to sensitivity, the data presented suggest that the test is sufficiently sensitive to be of clinical value. In this connexion an argument frequently used as a condemnation of all liver function tests needs to be refuted. It is based on hepatectomy experiments, and concludes from the fact that a 70 per cent. hepatectomy produces few symptoms (Mann and Power, 1935) that the reserve power of the liver is too great to allow the demonstration of hepatic dysfunction, except as a terminal phenomenon. This proposition ignores the great difference between a partial surgical removal and the action of poisons which may simultaneously attack all the liver cells. The fact that toxic jaundice can be a chronic condition, lasting for many years, is sufficient to dispose of this argument.

The nature of the function tested is important because it is desirable for many purposes to choose one which is independent of the excretion of bile. The excretory function is, of course, the easiest of all functions to test, and gross impairment is at once revealed by the presence of jaundice. Latent jaundice may be detected by the icterus index or Van den Bergh reaction, and the bromsulphalein excretion test is an even more sensitive index than these. Nevertheless these procedures suffer from the obvious limitation that they are all testing the same function, which may be impaired either by toxins or by biliary obstruction, and it is now generally agreed that the Van den Bergh (1918) reaction cannot be relied upon to distinguish the two types. The only hope of doing this at present is to test some other function, such as the galactose utilization function, which has no connexion with the secretion of bile. Moreover, there are many poisons which affect the glyco-genic function much more than the excretory one; the cases of Graves' disease reported above form an excellent example of this, for none of them was jaundiced. Many cases of cirrhosis of the liver also fall into this category. This point is further emphasized by Appendix II, which gives the serum-bilirubin concentration in the 16 cases of jaundice. It will be noted that the obstructive cases (with no impairment of galactose function) average 12.9 mg. of bilirubin per 100 c.c., while the toxic cases (all with impaired galactose function) have an average serum bilirubin of only 5.4 mg. per 100 c.c. The dissociation between the two tests is well marked.

The clinical value of the test, therefore, depends upon its power of testing one function of the liver which is independent of the excretion of bile. It would appear that this information may be useful for the following purposes:

(1) The demonstration of hepatic damage in diseases in which its presence is uncertain or unconfirmed, e.g. hyperthyroidism (see above), pneumonia (Curphey and Solomon, 1938), after surgical operations (Boyce and McFettridge, 1938), and rheumatoid arthritis (Rawls, Weiss, and Collins, 1937).

(2) The detection or confirmation of hepatic cirrhosis of all types. A few examples of this condition are included in this paper among those of toxic jaundice. The test is of particular value when jaundice is slight or absent.

(3) The differential diagnosis of toxic from obstructive jaundice. As noted above, the pigmentary tests are, in general, unreliable for this purpose, but as there is no obvious reason why galactose utilization should be impaired by biliary obstruction, at least in the early stages, the test should be of real value here. The cases of jaundice in this series are too few to reveal the limitations of the test in this respect, but they have at least failed to show any disagreement with the results expected, since all the toxic and none of the obstructive cases showed impaired function. The time factor is no doubt important in obstructive jaundice, and more data are required on this point, but case No. 62 provides an example of obstructive jaundice with normal liver function after eight weeks obstruction due to carcinoma of the pancreas.

#### *Summary*

(1) The principles involved in the clinical use of liver function tests are discussed, with special reference to the differential diagnosis of jaundice.

(2) Reasons are given why galactose is to be preferred to laevulose as an indicator of the glycogenic function of the liver.

(3) A modification of the galactose tolerance test is described in which the blood-galactose is estimated at intervals after an oral dose of 40 gm.

The term 'galactose index' (G.I.) is suggested for the sum of the four blood-galactose values, at  $\frac{1}{2}$ , 1,  $1\frac{1}{2}$ , and 2 hours, expressed in mg. per 100 c.c.

(4) Results are given for 50 normal persons, six cases of diabetes mellitus, six cases of obstructive jaundice, 10 cases of toxic jaundice, and 12 cases of hyperthyroidism. In normal persons the blood-galactose never exceeded 80 mg. per 100 c.c. and the G.I. did not exceed 160. The average normal G.I. was 68. Normal figures were recorded in diabetes and in obstructive jaundice, and impairment of function was demonstrated in toxic jaundice and in hyperthyroidism.

It is a pleasure to express my thanks to the honorary physicians and surgeons of the Westminster Hospital for permission to investigate cases under their care, and also to the John Burford Carlill trustees for financial assistance. Owing to war-time conditions the paper was written without the aid of a reference library, and it is feared that the bibliography may be incomplete. Apologies are offered to any writers whose papers may have been omitted from the discussion for this reason.

## APPENDIX I

Case.	Age.	Sex.	Blood-galactose in mg. %				G. I.	Diagnosis.
			$\frac{1}{2}$ hr.	1 hr.	1 $\frac{1}{2}$ hrs.	2 hrs.		
1	21	M	19	45	29	18	111	Normal student
2	21	M	24	63	23	0	110	" "
3	22	M	27	47	18	8	100	" "
4	22	M	39	32	16	12	99	" "
5	21	M	29	16	37	15	97	" "
6	22	M	30	41	10	8	89	" "
7	25	M	37	31	10	3	81	" "
8	22	M	32	39	8	2	81	" "
9	22	M	31	28	13	7	79	" "
10	21	M	24	53	0	0	77	" "
11	23	M	4	29	7	7	47	" "
12	20	M	19	19	5	3	46	" "
13	21	M	8	15	15	0	38	" "
14	22	M	18	10	3	3	34	" "
15	22	M	7	10	9	7	33	" "
16	22	M	5	10	7	7	29	" "
17	26	M	10	11	2	0	23	" "
18	21	M	5	13	0	0	18	" "
19	22	M	0	2	2	0	4	" "
20	23	M	0	3	0	0	3	" "
Controls.								
21	23	F	16	47	78	22	163	Haemorrhoids
22	32	F	65	81	9	5	160	Bacilluria
23	45	F	73	44	21	12	150	Angioma of lip
24	77	M	43	68	21	0	132	Arteriosclerosis
25	24	F	45	60	12	9	126	Bacilluria
26	40	F	22	66	16	11	115	Varicose veins
27	56	F	28	43	21	19	111	Mastectomy
28	36	F	28	38	9	33	108	Abdominal pain
29	37	F	72	9	5	0	86	Neurosis
30	28	F	35	25	15	3	78	Abdominal pain
31	47	F	23	26	12	10	71	Old cholecystectomy
32	33	F	40	13	10	5	68	Haemorrhoids
33	37	F	20	34	7	7	68	Haemorrhoids
34	31	F	22	15	18	12	67	Neurosis
35	28	F	19	18	12	13	62	Foot strain
36	27	F	9	12	23	17	61	Bacilluria
37	21	M	26	19	7	4	56	Abdominal pain
38	38	F	19	25	5	5	54	Abdominal pain
39	49	F	25	20	6	0	51	Menopause
40	51	F	19	28	3	0	50	Muscular strain
41	50	F	19	9	9	12	49	Neurosis
42	52	F	10	15	12	9	46	Menopause
43	60	F	0	17	19	10	46	Old cholecystectomy
44	52	F	9	24	12	0	45	Neurosis
45	51	F	18	18	4	2	42	Haemorrhoids
46	60	F	14	10	6	6	36	Asthma
47	53	F	22	10	2	0	34	Asthma
48	33	M	6	11	8	8	33	Neurosis
49	49	F	0	25	4	2	31	Varicose veins
50	26	F	12	3	3	0	18	Rectal abscess

Average for all normal subjects—68

## APPENDIX II

Case.	Age.	Sex.	Blood-galactose in mg. %				G. I.		Diagnosis.
			$\frac{1}{2}$ hr.	1 hr.	$1\frac{1}{2}$ hrs.	2 hrs.			
51	52	F	26	49	21	0	96		Diabetes mellitus
52	66	F	35	24	18	14	91		" "
53	67	F	23	31	8	13	75		" "
54	63	M	13	26	3	0	42		" "
55	—	M	8	18	15	0	41		" "
56	56	F	16	6	0	0	22		" "
57	50	F	21	58	37	28	144	6.8 mg. % bilirubin	Obstructive jaundice, gall-stones
58	71	M	44	43	22	11	120	—	Obstructive jaundice, gall-stones
59	71	M	26	32	34	37	129	15.7 mg. % bilirubin	Obstructive jaundice, carcinoma of pancreas
60	59	F	32	28	41	19	120	14.1 " "	Obstructive jaundice, carcinoma of pancreas
61	58	M	20	19	36	26	101	10.9 " "	Obstructive jaundice, glands in portal fissure
62	45	F	11	13	10	15	49	17.0 " "	Obstructive jaundice, carcinoma of pancreas
						Average 12.9 " "			
63	54	F	84	175	189	136	584	4.0 mg. % bilirubin	Toxic jaundice, hepatic cirrhosis
64	54	F	63	147	152	145	507	5.3 " "	Toxic jaundice, hepatic cirrhosis
65	59	M	120	132	78	37	367	11.6 " "	Toxic jaundice, catarrhal jaundice
66	50	F	19	72	103	93	287	12.2 " "	Toxic jaundice following atophan
67	66	F	60	86	83	39	268	2.2 " "	Toxic jaundice, catarrhal jaundice
68	47	M	49	107	74	32	262	3.0 " "	Toxic jaundice, hepatic cirrhosis
69	27	M	159	58	19	13	249	5.6 " "	Toxic jaundice, catarrhal jaundice
70	31	M	75	87	38	13	213	2.4 " "	Toxic jaundice following gold therapy
71	56	F	19	102	57	21	199	—	Toxic jaundice, hepatic cirrhosis
72	60	F	49	—	88	60	197	2.3 mg. % bilirubin	Toxic jaundice, hepatic cirrhosis
						Average 5.4 " "			
73	44	F	100	173	110	65	448	B.M.R. +75 %	Hyperthyroidism
74	46	M	126	147	60	19	352	" +78 "	"
75	42	F	129	119	75	5	328	" +53 "	"
76	18	F	44	97	105	66	312	" +52 "	"
77	42	F	81	128	78	5	292	" +58 "	"
78	25	F	110	73	66	0	249	" +53 "	"
79	24	F	60	96	44	13	213	" +73 "	"
80	42	F	44	68	81	18	211	" +20 "	"
81	34	F	69	91	40	11	211	" +62 "	"
82	41	M	149	36	9	5	199	" +37 "	"
83	17	F	49	58	5	0	112	" +39 "	"
84	13	F	22	13	16	25	76	" +56 "	"

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## NEW OBSERVATIONS ON THE AETIOLOGY AND PROGNOSIS OF ACHRESTIC ANAEMIA<sup>1</sup>

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With Plate 5

IN 1935 we published preliminary reports, and in 1936 a full account, of a disease which we termed achrestic anaemia. The patients had a blood picture exactly resembling that of Addisonian pernicious anaemia and, as in this disease, the bone-marrow of the femur at the post-mortem examination showed a true megaloblastic hyperplasia. There were, however, three striking differences, (1) free HCl was found in the gastric juice, (2) the patients showed a progressive and eventually complete failure to respond to anti-pernicious anaemia treatment, so that the course of the disease was downward leading to death, (3) adequate amounts of the anti-anaemic principle were shown to be present in the liver.

Since the gastro-hepatic apparatus for the production and storage of the anti-anaemic principle seemed to be in order, yet the erythropoietic tissue showed changes known to be due to deprivation of the principle, we suggested that the aetiology of this disease was a failure to utilize the principle or to mobilize it from the tissue stores.

It was clear that if this suggested aetiology were correct, patients showing the same failure to respond to specific treatment, but having achlorhydria, would be found; such a case was reported by us in 1938. In practice the achlorhydric cases have proved to be extremely rare; achrestic anaemia as originally described has been seen about once to every 100 patients with pernicious anaemia, but only one example of achrestic anaemia with achlorhydria has been discovered among a series of more than 1,100 patients with pernicious anaemia. We prefer, therefore, to keep the name achrestic anaemia for the condition originally described.

Since 1936, cases of achrestic anaemia have been reported by Abrahamson and Thompson (1937), Wauchope and Leslie-Smith (1938), and Hynes (1939). Dameshek and Valentine (1937) noted two cases of pernicious anaemia relapsing while under treatment which were probably of this type, and Davidson and Fullerton (1938) described a patient whom they thought might have had achrestic anaemia.

On the other hand, the separation of achrestic anaemia has been criticized

<sup>1</sup> Received October 27, 1939.

on several grounds, the most important of which have concerned the changes in the bone-marrow. In order to meet these criticisms and clarify the diagnosis of achrestic anaemia, six new cases have been studied, and particular attention has been paid to the pathology of the bone-marrow. Since all the patients are still alive the marrow has been studied by the method of sternal biopsy; there was a true megaloblastic hyperplasia in all of them. New information has also been obtained about the prognosis of the disease in younger patients.

### *Case Reports*

*Case 1.* A business man, aged 58 years, attended the out-patient clinic on January 22, 1938, complaining of loss of energy, constipation, abdominal discomfort, flatulence, lack of appetite, and nausea. These complaints had been present for about six months, but in the last three months pallor and yellowness of the face had been noticed. There was dyspnoea and palpitation on exertion and slight loss of weight; paraesthesiae of hands and feet were not present; micturition was normal. There was nothing noteworthy in the previous medical or family histories. Physical examination was largely negative; the colour was pale yellow; neither liver or spleen were palpable, nor were there any enlarged lymph nodes. The central nervous system was normal. The abdomen was rather distended, and there were some rhonchi at the bases of the lungs. The heart was not enlarged; the blood-pressure was 125/75 mm. The urine contained no pathological constituents. The blood count was: red cells 2,010,000 per c.mm.; haemoglobin 45 per cent.; colour index 1.13; white cells 2,200 per c.mm.; polymorphonuclears 83, lymphocytes 12.5, monocytes 2.5, eosinophils 1.5, basophils 0, myelocytes 0.5, per cent.; no nucleated red cells. The patient was admitted to hospital, and the following investigations were made:

Fractional gastric analysis, after 0.25 mg. histamine, showed free acid present—0 (fasting contents), 23.7, 32, 19 units respectively in successive 10-minute samples. Wassermann reaction negative. Van den Bergh reaction, 'direct delayed', serum contained 2.2 units bilirubin. Price-Jones curve—mean red-cell diameter 7.87 microns, megalocytosis 19 per cent., microcytosis 0. Sternal puncture showed a very active and cellular marrow containing 16.6 per cent. megaloblasts, and 26.4 per cent. normoblasts (see Table VII). When he was admitted on February 5 his blood count (see Table I) had fallen considerably. He was given three courses of 12 c.c. each of a liver extract (Pernaemon); although a reticulocyte rise (maximum 19.8 per cent.) occurred after each course, the improvement was very slow, and for a time the anaemia actually became worse. After five weeks, recovery set in and the patient was discharged to the convalescent hospital on March 28 with red cells 2,064,000 per c.mm. and haemoglobin 55 per cent. He was given 1 oz. of desiccated hog's stomach daily during his stay and after his discharge and he improved steadily. By July, 1938, his blood count was practically normal, and remained so until May, 1939, when he complained that his symptoms were returning in spite of regular maintenance of treatment; investigation showed that the red cells had fallen to 2,670,000 per c.m., and haemoglobin to 64 per cent. He also complained of attacks of abdominal pain accompanied by a 'feeling of obstruction' in the left iliac fossa and constipation, but not of diarrhoea, or blood or slime in the motions. He

was readmitted to hospital, but radiographic examination of the alimentary tract did not disclose any evidence of organic disease. Since his blood count had fallen considerably, and now failed to respond to liver treatment, a blood transfusion of 1,800 c.c. was given by the drip method. This had very good results, and on August 3 his haemoglobin was 74 per cent. After discharge, treatment with liver extract and hog's stomach was resumed and the blood level has improved still further.

TABLE I

Date.	Red cells millions per c.mm.	Hb. %	Colour index.	White cells per c.mm.	Reticulo- cytes %	Treatment.
1938						
Jan. 22	2.010	45	1.13	2,200	—	—
Feb. 5	1.620	35	1.09	5,000	1.6	—
„ 19	1.048	26	1.24	3,400	11.2	I.m. liver
„ 23	1.128	28	1.23	3,400	5.8	„
Mar. 3	1.088	28	1.25	2,800	19.8	„
„ 18	1.658	44	1.30	3,400	9.7	„
„ 31	2.064	55	1.30	3,300	7.9	„
Apr. 28	2.944	75	1.29	7,200	1.6	Des. stomach
May 31	3.340	82	1.24	3,600	—	„
Aug. 23	4.208	96	1.14	6,200	—	„
Oct. 4	4.460	99	1.11	4,800	—	„
Dec. 29	4.160	96	1.15	5,000	—	„
1939						
Mar. 2	4.380	98	1.12	4,600	—	„
Apr. 13	4.100	90	1.10	4,000	—	„
May 25	2.670	64	1.20	4,200	—	„
June 21	1.890	44	1.15	2,800	1.0	I.m. liver
July 19	1.120	27	1.22	2,200	1.8	„
Aug. 23	3.460	70	1.01	7,000	2.2	Transfusion + I.m. liver
Sept. 25	4.600	97	1.05	6,400	1.0	Des. stomach + I.m. liver

*Case 2.* A clerk, aged 42 years, was admitted to the Manchester Royal Infirmary on March 11, 1938. For the past three months he had been complaining of weakness, excessive fatigue, and loss of appetite. His tongue and mouth were sore; attacks of nausea and vomiting had occurred at night, while dyspnoea on exertion had become troublesome. The bowels were regular and micturition normal. He had lost 14 lb. in weight during the previous four months. Between 1914 and 1918 he had had malaria, dysentery, and typhoid fever, but there had been no recurrences. In January, 1937, he had been treated for a skin lesion affecting hands, legs, and face for about six weeks. On examination he was seen to be a thin man who had obviously lost weight; he had a pale, muddy complexion, and was edentulous with complete dentures. The tongue was smooth, moist, and shiny, and the throat appeared to be normal. In the abdomen the spleen was just palpable, the liver was not enlarged, and there were no abnormal masses or areas of tenderness. The pulse was 80, regular and full; the heart was not enlarged, there was a generalized soft systolic murmur. Blood-pressure was 115/80 mm. There was nothing unusual in the lungs, central nervous system, or urine. On the back of the hands was a rash of small, reddish raised areas, which appeared to be a low grade septic infection.

The Wassermann reaction was negative. The serum contained 0.8 units of bilirubin. A fractional test meal showed the presence of free HCl—0 (fasting contents), 0, 0, 11, 36, 39, 39 units respectively in successive 15-minute samples. The blood count was: red cells 2,816,000 per c.mm.;

haemoglobin 68 per cent.; colour index 1.19; white cells 3,200 per c.mm.; polymorphonuclears 78.5, lymphocytes 18.5, monocytes 2.0, eosinophils 1, basophils 0, per cent.; no nucleated red cells; reticulocytes 6.4 per cent. The Price-Jones curve showed a mean red-cell diameter of 8.12 microns, megalocytosis 19.6 per cent., microcytosis 0. Sternal puncture (Table VII) showed a cellular active marrow with 11.2 per cent. megaloblasts and 18 per cent. normoblasts. Radiography of the alimentary tract revealed no organic lesion.

TABLE II

Date.	Red cells millions per c.mm.	Hb. %	Colour index.	White cells per c.mm.	Reticulo- cytes %	Treatment.
1938						
Mar. 11	2.816	68	1.19	3,200	6.4	—
" 25	2.816	70	1.24	3,400	4.5	Des. stomach
Apr. 28	3.296	82	1.24	6,200	2.9	"
May 26	3.430	83	1.21	5,200	3.0	"
July 7	3.370	84	1.24	4,600	—	"
Oct. 13	3.620	86	1.20	4,800	0.6	"
Dec. 9	3.080	78	1.26	5,600	—	"
1939						
Jan. 6	3.250	82	1.25	4,600	—	" + I.m. liver
Mar. 14	1.960	55	1.37	3,000	—	I.m. liver
Apr. 20	1.740	47	1.34	2,400	1.2	"
May 4	1.390	38	1.34	4,600	10.8	"
" 19	1.688	45	1.34	2,800	0.7	"
" 26	1.306	36	1.35	2,200	0.7	—
June 3	2.452	58	1.18	2,000	—	Transfusions
" 26	2.450	57	1.17	4,200	—	I.m. liver
July 22	1.670	40	1.18	4,000	—	"
Aug. 3	3.550	78	1.11	1,000	—	Transfusions
Sept. 18	2.780	66	1.12	2,400	0.9	Des. stomach + I.m. liver

He was given desiccated hog's stomach (1 oz. daily) and, although the blood count had improved only slightly, the patient felt better. On March 28 he was discharged to the convalescent hospital, and three weeks later to his home, the same treatment being continued. His blood count (Table II) improved, but in May, 1938, he had some troublesome diarrhoea which was successfully treated. In December, 1938, he complained of vomiting, and treatment was augmented with regular doses of intramuscular liver extract. There was slight improvement in the blood count in January, 1939, and he felt well again, but in March he was very much worse; diarrhoea was severe, and the blood count had fallen to 1,960,000 red cells per c.mm. and 55 per cent. haemoglobin. In spite of increased doses of intramuscular liver extract his blood count and clinical condition became worse and he was readmitted to hospital.

The sternal marrow again proved to be very cellular, but primitive erythroblasts were much more numerous (Table VII; Plate 5, Fig. 1); pro-erythroblasts were 10 per cent., megaloblasts 28.2 per cent., and normoblasts 4.4 per cent.; the curiously shaped metamyelocytes seen in pernicious anaemia were numerous.

He was given 6 c.c. of Pernaemon Simplex intramuscularly daily for four days, and repeated weekly. At first (see Table II) there was a small reticulocyte response (maximum 12.5 per cent.) and the blood count improved slowly, while his general condition also improved. Later, in spite of treatment, the blood count fell almost to its previous level, and he was given

three blood transfusions (Group 0; 600 c.c. each). The results were good and he was discharged on June 9, 1939, continuing treatment with 4 c.c. intramuscular liver extract twice weekly. The blood count fell slowly, and between July 22 and August 3 further blood transfusions were given, total 1,800 c.c. He is fairly well at present, although the blood level has again slightly diminished.

TABLE III

Date.	Red cells millions per c.mm.	Hb. %	Colour index.	White cells per c.mm.	Reticulo- cytes %	Treatment.
1939						
May 20	2.546	60	1.17	5,600	—	—
June 2	2.270	54	1.17	7,600	1.6	I.m. liver
„ 9	2.360	55	1.17	5,400	8.4	„
„ 16	2.478	59	1.18	4,000	9.6	„
„ 29	2.778	68	1.17	5,400	—	„
July 20	3.580	88	1.22	6,400	2.0	„
Sept. 5	4.440	99	1.12	9,400	1.6	„

*Case 3.* A male store-keeper, aged 27 years, was seen in the clinic on May 20, 1939. For the previous two months he had complained of increasing weakness and fatigue, and had had difficulty in carrying on with his work. Palpitation and dyspnoea were troublesome and his appetite was poor, but there was no flatulence, abdominal pain, or discomfort. The bowels were constipated and he had had haemorrhoids which had bled occasionally for four years.

Five years previously he had been in another hospital suffering from 'anaemia' with symptoms similar to the present, and he had been given a prolonged course of liver injections, with considerable improvement. There was nothing noteworthy in the family history. Examination showed a well-nourished young man, pale and slightly yellow in colour. The tongue was smooth but not sore and his teeth were carious; the throat and tonsils were slightly injected. The pulse was 84, regular, and of good volume. The spleen and liver were just palpable. Rectal examination showed small haemorrhoids. The heart, which was not enlarged, had an apical systolic murmur. The blood-pressure was 115/75 mm. A few scattered rhonchi were heard in the lungs, but air entry was good throughout. There was nothing unusual in the central nervous system or urine. The blood count was: red cells 2,546,000 per c.mm.; haemoglobin 60 per cent.; colour index 1.17; white cells 5,600 per c.mm.; polymorphonuclears 83.5, lymphocytes 14, monocytes 1.5, myelocytes 1 per cent.; no nucleated red cells.

Fractional gastric analysis showed free HCl present—0 (fasting contents), 0.6, 8, 21, 16, 0 units respectively in successive 15-minute samples.

The sternal marrow (Table VII) was very cellular and contained 4.4 per cent. normoblasts and 34.4 per cent. megaloblasts (Plate 5, Fig. 2). The Price-Jones curve showed a mean red-cell diameter of 7.45 microns, megalocytosis 1.2 per cent., microcytosis 1.2 per cent. The serum contained 1.3 units of bilirubin. The Wassermann reaction was negative. He was given concentrated liver extract (Pernaemon Forte) intramuscularly in large doses and improved slowly (see Table III), the reticulocytes rising to a maximum of 12.4 per cent. He was discharged four weeks later to the convalescent hospital where the treatment was continued. After leaving hospital the treatment was maintained and his progress was steady and satisfactory.

*Case 4.* A stewardess (single), aged 20 years, was first seen at the clinic



on May 17, 1938. She complained of fatigue, lassitude, weakness, 'cramps' in the legs, and indigestion, but not palpitation, dyspnoea, nausea, or vomiting. The bowels were constipated and she had irregular amenorrhoea, having had no period between September 1937 and March 1938, and only one scanty one since March; there was no dysmenorrhoea. The illness was of some months duration and, owing to the presence of a cough and pleurisy,

TABLE IV

Date.	Red cells millions per c.mm.	Hb. %	Colour index.	White cells per c.mm.	Reticulo- cytes %	Treatment.
1938						
May 17	1-980	64	1-69	5,600	1-4	I.m. liver and iron
June 14	2-760	68	1-23	10,400	2-8	"
July 19	2-470	68	1-36	6,600	—	"
Aug. 16	2-156	60	1-38	3,400	3-6	"
" 30	1-808	50	1-39	4,000	—	"
Sept. 19	1-950	53	1-39	4,800	6-8	I.m. liver
Oct. 3	2-710	72	1-33	5,600	7-0	"
" 20	2-940	80	1-35	4,600	—	"
Nov. 3	3-420	92	1-36	5,800	—	"
Dec. 2	3-520	86	1-23	4,200	—	"
" 30	3-250	81	1-24	6,200	—	"
1939						
Apr. 28	2-870	74	1-28	4,200	—	"
June 9	2-220	65	1-46	5,400	—	"
July 14	2-820	77	1-32	3,800	—	"
Aug. 25	3-110	81	1-30	6,400	1-0	"
Sept. 22	3-200	83	1-29	9,600	0-8	"

tuberculosis had been suspected. Radiography, however, had not revealed any evidence of tuberculous infection. Examination showed a pale, rather thin, but not wasted girl. The various systems presented nothing unexpected; neither spleen nor liver were palpable and there were no enlarged lymph nodes. The blood count showed: red cells 1,980,000 per c.mm.; haemoglobin 64 per cent.; colour index 1-69; white cells 5,600 per c.mm.; polymorphonuclears 69, lymphocytes 27, monocytes 2, eosinophils 2, basophils 0 per cent.; no nucleated red cells; reticulocytes 1-4 per cent. The Price-Jones curve showed a mean red-cell diameter of 7-75 microns, megalocytosis 12 per cent., microcytosis nil. Fractional gastric analysis (gruel + 0-25 mg. histamine subcutaneously) showed free HCl—10 (fasting contents) 27, 42, 29, 13, 7 units respectively in successive 15-minute samples.

As the patient did not wish to come into hospital, she was given 2 c.c. intramuscular liver extract (Neo-hepatex) twice weekly and large doses of iron. For a time the patient improved and the blood counts (Table IV) showed a rise. On August 30, however, there was a definite fall, although treatment had been scrupulously maintained. Sternal puncture (Table VII; Plate 5, Fig. 3) showed a very cellular active marrow with 4-2 per cent. normoblasts, 20-8 per cent. megaloblasts, and 12-8 per cent. pro-erythroblasts. This time she agreed to come into hospital. The serum contained 0-5 units of bilirubin, the Wassermann reaction was negative, and the red-cell fragility was within normal limits.

She was given intensive treatment with a concentrated intramuscular liver extract (Pernaemon Forte), and although the reticulocytes never rose very high (maximum 9-1 per cent.), there was a steady improvement. On October 10 she was discharged to the convalescent hospital where treatment was maintained, and when she left there on November 3 the red cells were



3,420,000 per c.mm. and haemoglobin 92 per cent. This level was maintained for a time after her discharge and treatment with liver extracts (2.5 c.c. weekly) was continued. In June, 1939, she reported that menstruation had returned and she felt very well, but as the blood count was lower, increased doses of liver extract (5 c.c. weekly) were recommended. This had the desired effect; her blood count rose and remained at a satisfactory level, progress after this date being uneventful.

*Case 5.* A female packer, aged 17 years, was first seen in the clinic on August 3, 1937. In March, 1937, she had been in hospital on account of tetanic spasms of the hands; investigation had not revealed any cause, and the tetany had not recurred. Since that time increasing pallor had been noticed and she had complained of loss of energy, loss of appetite, faintness, dizziness, headaches, dry cough, and soreness of tongue. The bowels and menstruation were regular; she had had rickets when very young, and diphtheria in 1936. In this family there were two other children both healthy, and neither had had rickets. The mother had had seven miscarriages, all following the birth of the patient. Examination: she was a pale, rather yellow, but well nourished girl. The upper central incisors were large and notched, resembling Hutchinson's teeth. The tongue was clean and not smooth; the throat was healthy and the tonsils slightly enlarged. The pulse was 100, regular and full. In the abdomen the spleen was just palpable, but not the liver. The heart was slightly enlarged to the left and a systolic bruit was audible all over the praecordium. The blood-pressure was 130/80 mm. There was nothing unusual to be found in the lungs, central nervous system, or urine. The skin of the legs was discoloured below the knees. The blood count was: 1,490,000 per c.mm.; haemoglobin 33 per cent.; colour index 1.10; white cells 4,600 per c.mm.; polymorphonuclears 76.5, lymphocytes 19.5, monocytes 4 per cent.; nucleated red cells 1 per 100 white cells; reticulocytes 0.9 per cent.

She was admitted to hospital and a fractional test meal showed the presence of free HCl—0 (fasting contents), 0, 3, 12, 0 units respectively in successive 15-minute samples. The Price-Jones curve showed a mean red-cell diameter of 7.71 microns with megalocytosis 12 per cent., microcytosis nil.

Sternal puncture showed a very cellular marrow with numerous primitive cells, 26.6 per cent. megaloblasts, and 1.6 per cent. normoblasts (Table VII; Plate 5, Fig. 4). The Wassermann reaction was repeatedly negative. The serum-bilirubin was 1.0 unit; serum-calcium 8.9 mg. per 100 c.c.; blood-urea 24 mg. per 100 c.c. The total fat content of the faeces was 22.6 per cent., combined fatty acids 15, free fatty acid 4.6, neutral fat 3 per cent. Radiograms of the skull showed a diffuse hyperostosis of the skull, particularly in the parietal region; this was quite different from that recorded in cases of Cooley's anaemia and the radiologist thought it might be syphilitic. The parents' Wassermann reactions were negative.

The patient was given intramuscular liver extract, but in spite of this her condition deteriorated so rapidly that blood transfusion was necessary. A transfusion (Group A) of 500 c.c. was given, and another similar one a week later. Intramuscular liver extract was then given in doses of 2 c.c. daily for ten days. The reticulocytes rose to a maximum of 17.3 per cent. A sternal puncture on August 31 (Table VII; Plate 5, Fig. 5) showed that, as in pernicious anaemia, the megaloblasts had practically disappeared, but normoblasts were now present in large numbers, 28.6 per cent. She made

steady progress (see Table V), further liver treatment was given, and on September 10 she was discharged to the convalescent hospital with a red-cell count 3,710,000 per c.mm., haemoglobin 64 per cent.

After discharge she was treated with desiccated stomach (Pepsac, 1 oz. daily) and iron preparations. She remained well until late in January, 1938, when she was unable to take the stomach preparation on account of vomiting,

TABLE V

Date.	Red cells millions per c.mm.	Hb. %	Colour index.	White cells per c.mm.	Reticulo- cytes %	Treatment.
1937						
Aug. 3	1.490	33	1.10	4,600	0.9	—
" 11	0.720	15	1.08	—	0.9	I.m. liver
" 19	2.030	38	0.95	7,400	1.2	Transfusion
" 30	2.340	44	0.95	5,600	17.3	I.m. liver
Sept. 10	3.710	64	0.87	5,200	2.7	"
Oct. 29	4.120	80	0.98	6,800	—	"
Nov. 26	4.568	85	0.92	7,400	—	Des. stomach + iron
1938						
Jan. 4	3.890	82	1.06	9,400	—	"
Feb. 25	1.855	42	1.13	7,000	0.4	"
Mar. 21	1.200	26	1.08	5,600	8.0	I.m. liver
" 28	2.735	56	1.03	7,200	9.0	I.m. liver + transfusion
Apr. 28	3.560	74	1.06	5,400	—	I.m. liver
May 26	4.010	78	0.98	6,600	—	"
June 28	2.030	45	1.10	2,800	—	"
July 5	2.420	54	1.12	9,800	21.2	"
" 26	3.180	72	1.13	5,000	—	"
Aug. 30	2.770	69	1.23	5,800	—	"
Sept. 26	3.410	80	1.18	7,000	—	Des. stomach
Nov. 7	2.910	70	1.20	6,800	—	"
Dec. 13	2.568	58	1.13	4,200	—	"
1939						
Jan. 9	1.624	38	1.18	2,600	—	"
" 17	0.805	17	1.06	2,600	0.9	"
" 23	2.650	52	0.99	1,500	0.8	Transfusion + I.m. liver
Feb. 6	2.975	62	1.04	5,400	8.5	I.m. liver
Mar. 8	4.270	90	1.05	7,600	—	"
Apr. 19	4.820	98	1.01	5,600	—	"
May 24	4.510	90	1.00	8,600	—	"
July 6	3.970	86	1.08	5,000	1.2	"
Aug. 17	4.440	89	1.00	4,600	—	"
Sept. 28	3.940	82	1.05	6,600	—	"

and the treatment was changed to intramuscular liver extract, but her condition deteriorated and she was readmitted on March 3, 1938, for intensive treatment. A total of 32 c.c. of a concentrated liver extract was given, but after three weeks the blood count had fallen still further; a drip transfusion of 2,000 c.c. was given and at the same time a rise in reticulocytes occurred (maximum 19 per cent); the combined effects caused great improvement which was maintained without further transfusion. After discharge, treatment with liver extract was resumed and the patient remained well until June, 1938, when the blood count again began to fall; there was also trouble with the transfusion wound on the left leg which had ulcerated and would not heal. A different liver extract was substituted and the blood count rose to 72 per cent. haemoglobin. But on September 2 she suddenly had a typical and severe anaphylactic shock following an injection of the same liver extract as she had had previously. Wheal experiments with six different brands showed that she was highly sensitive to all of them. The

treatment was changed to an oral preparation and her condition remained reasonably satisfactory. In December, 1938, as the leg wound still had not healed, Mr. F. H. Bentley applied skin grafts, which took well and the wound healed. A Kahn reaction taken at this time was negative.

In January, 1939, she had several fainting attacks and there was severe and prolonged epistaxis. The blood count fell very rapidly and on January 17 there were only 805,000 red cells per c.mm. with haemoglobin 17 per cent. She was again admitted to hospital and sternal puncture (Table VII) showed that the marrow was still hyperplastic and had reverted to the megaloblastic type; there were 24.4 per cent. megaloblasts. A transfusion of 2,500 c.c. was given by the drip method, and intramuscular liver extract was given after a test dose had failed to show anaphylactic phenomena. She made a good recovery and there was no further epistaxis. Radiograms of the skull and long bones at this time showed that the hyperostosis of the parietal and frontal bones was unchanged and that the long bones were not affected. She went home on March 8 with a blood count of 4,270,000 red cells per c.mm., haemoglobin 90 per cent. With regular intramuscular injections the patient remained quite well until May 24, when she complained of malaise and weakness and on examination was found to have a pericardial effusion; the blood count was quite satisfactory. She was again taken into hospital and the effusion was verified by radiography. Anti-anaemic treatment was maintained and by June 22 she was well enough to leave for the convalescent hospital. Her subsequent progress was satisfactory and the blood count remained steady, the same treatment being given.

*Case 6.* A married woman, aged 25 years, a packer in a mineral water factory, was first seen in the out-patient department on June 7, 1939. She complained of weakness, undue fatigue, loss of weight, increasing pallor and yellowness of about two months' duration; she had ceased work a week previously. The bowels were regular, micturition normal, and menstruation regular but scanty. There were no haemorrhages or rashes. She had been married five years, but there were no children. Her previous medical history included diphtheria at eight, mastoid operation and tonsillectomy at fifteen years. Two sisters were said to be anaemic, but no other relatives were affected. On examination she proved to be a well-nourished young woman, but very pale and icteric. The tongue was smooth and moist; the throat injected; she was edentulous, but had complete dentures. The pulse was 120, regular, and of good volume. There was no koilonychia. The spleen was not palpable, the liver could just be felt, and there were no enlarged lymph nodes. The heart was normal in size, but had a generalized haemic murmur. The blood-pressure was 150/70 mm. The lungs and central nervous system were normal. The urine contained no bile or other pathological constituents. The blood count was: red cells, 1,790,000 per c.mm.; haemoglobin 40 per cent.; colour index 1.11; white cells 4,000 per c.mm.; polymorphonuclears 52, lymphocytes 44.5, monocytes 3.5, per cent.; no nucleated red cells; reticulocytes 17 per cent. The Wassermann reaction was negative. The serum gave a direct delayed Van den Bergh reaction, and contained 2.5 units of bilirubin. Fractional gastric analysis showed the presence of free HCl—0 (fasting contents), 0.4, 12, 13, 12, 10 units respectively in successive 15-minute samples. The fragility of the red cells was not increased; haemolysis began in 0.44 per cent. NaCl, and was complete in 0.34 per cent. The Price-Jones curve showed a mean red-cell diameter of 7.6 microns, megalocytosis 11.6 per cent., microcytosis nil. Sternal puncture (Table VII; Plate 5, Fig. 6)

showed a hyperplastic marrow containing 27 per cent. megaloblasts and 9 per cent. normoblasts. She was given large doses of intramuscular liver extract and her blood count showed improvement (Table VI). On July 13 she was sent to the convalescent hospital where treatment was continued. After two weeks her haemoglobin had risen to 84 per cent. and she was sent home, treatment with intramuscular liver extract being maintained. The blood count has improved further, and her clinical condition is satisfactory.

TABLE VI

Date.	Red cells millions per c.mm.	Hb. %	Colour index.	White cells per c.mm.	Reticulo- cytes %	Treatment.
1939						
June 7	1.790	40	1.11	4,000	17.0	—
" 22	1.765	41	1.16	4,200	10.7	—
" 29	1.900	47	1.17	6,400	3.6	I.m. liver
July 6	2.500	58	1.11	5,200	8.6	"
" 27	3.688	84	1.14	6,800	—	"
Sept. 7	4.300	97	1.13	3,600	—	"
Oct. 5	4.220	93	1.10	6,200	1.7	"

#### Discussion

The six patients described all presented the features originally described by us as characteristic of achrestic anaemia, namely, a hyperchromic megalocytic anaemia, megaloblastic hyperplasia of the bone marrow, free HCl in the gastric juice, and a variable response to liver therapy. They have been arranged in two groups; cases 1 to 3 closely resemble the original patients, and cases 4 to 6 in which the syndrome has occurred in young women. This latter group resembles in some respects the so-called 'pernicious anaemia of pregnancy'; none of our patients were pregnant, but their response to liver treatment was better than in the first group, and their progress raises the hope that the prognosis, like that of pernicious anaemia of pregnancy, will also be better than that of our previous cases. The resemblance to pernicious anaemia of pregnancy is interesting, but it must be pointed out that in our experience true pernicious anaemia of pregnancy, i.e. a megalocytic anaemia with megaloblastic hyperplasia of the marrow and free HCl in the gastric juice, is rare; a high colour index, even megalocytosis, is not uncommon in severe pregnancy anaemia, but megaloblastic change in the marrow is very uncommon.

The patients described are, on the average, younger than those previously recorded, but this does not clash with our suggestion that achrestic anaemia is allied to pernicious anaemia, since the latter disease is now known to occur at an earlier age than was formerly thought; out of a series of 1,200 patients fully studied by one of us (J. F. W.), 36 were 30 years or younger; it is noteworthy that 25 of these were women, the youngest being 22 years of age when first seen.

Some authors have found difficulties in the differential diagnosis of achrestic anaemia. Vaughan (1936) classifies it with megalocytic anaemia due to liver disease, but the autopsies of our previously reported cases failed to show any lesion in the liver apart from the fatty changes common to all

prolonged anaemias. It is also becoming increasingly doubtful whether the megalocytic anaemia accompanying some cases of liver disease is due to megaloblastic change in the marrow; we have yet to see a verified case. Mørgensen (1938) follows Vaughan, but on the grounds that three out of the four published Price-Jones curves of achrestic anaemia cannot be separated into the components which he finds typical of pernicious anaemia. Mørgensen,

TABLE VII

*Sternal Marrow Puncture in Achrestic Anaemia*

(Results expressed as percentages of total nucleated cells)

Case No.	1	1	2	2	3	4	5	5	5	6
Date	22.3.38	21.6.39	17.3.38	24.4.39	1.6.39	30.8.38	17.3.37	31.3.37	17.1.39	28.6.39
Haemocyto blasts	4.4	3.0	4.0	5.8	7.2	10.6	24.0	1.2	3.4	2.0
Pro-erythro blasts	6.6	9.8	7.4	10.0	9.0	12.8	21.0	3.6	5.6	8.0
Normoblasts (total)	26.4	7.8	18.0	4.4	4.4	4.2	1.6	28.6	3.0	9.0
Type A	7.0	1.0	6.0	0	0	0	0	5.0	0	1.8
B	15.2	3.2	8.4	1.4	3.2	1.4	0.6	15.6	1.6	5.4
C	4.2	3.6	3.6	3.0	1.2	3.8	1.0	8.0	1.4	1.8
Megaloblasts (total)	16.6	15.2	11.2	28.2	34.4	20.8	26.6	0.8	24.4	27.0
Type A	1.0	9.0	2.6	9.6	21.4	7.0	15.6	0.2	17.2	14.4
B	10.4	3.6	6.2	4.0	9.6	8.8	9.8	0.2	6.8	9.6
C	4.2	3.6	3.6	3.0	1.2	3.8	1.2	0.4	0.4	3.0
Polymorphonuclears	17.0	24.0	28.0	12.2	20.6	20.0	5.4	34.8	26.0	24.8
Eosinophils	3.6	5.6	3.0	1.4	2.0	3.0	3.4	4.2	4.4	0.8
Basophils	0.4	0.6	0.4	0.2	0.4	0	0	1.0	0	0
Metamyelocytes	7.8	10.6	13.0	14.4	8.8	7.6	9.8	10.8	7.6	12.2
Myelocytes	14.8	19.6	13.0	18.6	11.0	14.0	4.0	12.4	7.8	12.2
Myeloblasts	0	0	0	0	0	0.6	0	0	0.2	1.2
Lymphocytes	1.6	2.6	2.0	4.2	2.0	4.4	2.0	2.4	16.0	2.2
Plasma cells	0.4	1.2	0	0.6	0.2	0.6	1.2	0.2	1.6	0.6
Monocytes	0	0	0	0	0	0.4	2.0	0	0	0

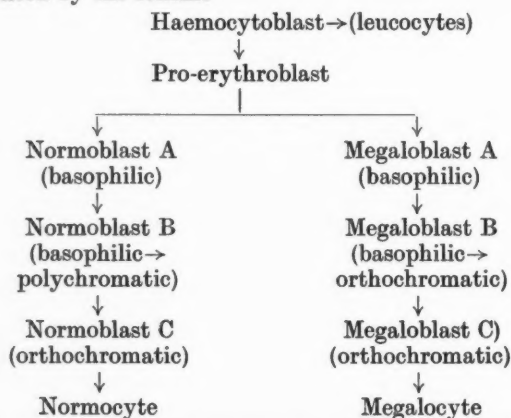
however, does not press the specificity of his theory since he has examined only 16 cases of pernicious anaemia of his own. It will be seen from Table VII that the bone-marrow changes in achrestic anaemia often show a mixture of normoblastic and megaloblastic hyperplasia—corresponding to the partial response to liver—which is not like that of pernicious anaemia in relapse. If the Price-Jones curve is thought to reflect changes in the marrow, it is not surprising that the curves of achrestic anaemia do not at all times resemble those of pernicious anaemia in relapse. Dyke and Young (1938) think that achrestic anaemia is related to megalocytic haemolytic anaemia. The differentiation of achrestic anaemia from haemolytic anaemias was dealt with in our 1936 paper, and it is sufficient to note here that in haemolytic anaemias the marrow shows an exclusively normoblastic hyperplasia (Israëls, 1939; Scott, 1939).

The chief difficulty, however, has been the differentiation of achrestic and aplastic anaemias; Castle and Minot (1936), Zanaty (1937), Davidson and Fullerton (1938), and Schulten (1939) have all classified the two conditions together. This confusion has apparently two sources. In the first place it has been recognized for some time that the symptoms of classical aplastic anaemia may occasionally be associated with a hyperplastic marrow. This hyperplasia



is often patchy but may be widespread, it may give place to aplasia during the course of the disease, or it may persist to the end; Scott (1939) recorded the results obtained by sternal puncture in such patients. But even when there is generalized hyperplasia, no megaloblasts occur in the marrow of patients with aplastic anaemia. Pro-erythroblasts and early normoblasts (Naegeli's 'macroblasts') may be present, usually only in small numbers, but the whole marrow picture, whether studied by sternal puncture during life or in post-mortem sections, is strikingly different from that of achrestic anaemia. The marrow picture in aplastic anaemia never resembles that of pernicious anaemia, while in achrestic anaemia the resemblance to pernicious anaemia is close.

The second source of confusion is in the nomenclature of the erythroblastic cells. This has been dealt with in detail by Israëls (1939), and his nomenclature has been used in this paper. Here it must be noted that the term 'megaloblast' is confined to a series of cells with distinctive nuclear structure—first described by Ehrlich—which occur typically in pernicious anaemia in relapse. These megaloblasts do not appear to take part in the normal formation of red blood-cells in extra-uterine life; normal formation occurs solely by maturation of the normoblasts. Israëls (1939) has suggested that the two groups have a common ancestor and that red blood-cell development can be represented by the scheme



The name 'megaloblast' has, however, been used by others to denote an early stage in the normal development of the red blood-cell, corresponding to the pro-erythroblast of the above scheme. Since such cells may be found in the marrow of patients with aplastic anaemia, as well as in pernicious and achrestic anaemias, it is not surprising that those who use this nomenclature confuse the two groups.

The sternal marrow biopsies now reported confirm the autopsy findings described earlier that the marrow changes in achrestic anaemia resemble those of pernicious anaemia. The records of case 5 show that, as in pernicious anaemia, the megaloblasts in the marrow are diminished, and early normo-



blasts appear when there is a response to liver treatment. The biopsy reports also show sometimes the mixture of normoblastic and megaloblastic hyperplasia which is seen in pernicious anaemia when inadequately treated. The findings are consonant with our original suggestion that achrestic anaemia is due to some interference with the proper action of the anti-pernicious anaemia liver principle on the erythropoietic tissues.

The correct differentiation of achrestic anaemia is important when treatment is considered. Specific antipernicious anaemia treatment should first be given; larger total doses are required than for pernicious anaemia, but they should be spread over a long period, and since there is some evidence that the more highly purified liver extracts now on the market may not contain all the active material, it is better to give one of the less highly purified intramuscular extracts. Blood transfusion seems to be necessary for the majority of patients sooner or later; in the young women it may be necessary only to tide over a specially difficult period (e.g. Case 5).

This may be contrasted with the treatment for aplastic or haemolytic anaemias. Antipernicious anaemia treatment is not indicated for either of these conditions, repeated transfusions being necessary in aplastic anaemia, while in haemolytic anaemia transfusion is often followed by a decision for splenectomy. Splenectomy has no place in the treatment of achrestic anaemia.

#### *Summary*

1. Six new cases of achrestic anaemia, a primary anaemia characterized by megalocytosis, free HCl in the gastric secretion, and megaloblastic hyperplasia in the bone-marrow, are described.

2. The bone-marrow was studied by sternal puncture. Typical megaloblasts in all stages were present; some of the patients also had early normoblasts during the course of the disease.

3. Three of the patients were young women; it is possible that the prognosis is more hopeful in such patients.

4. The differential diagnosis, especially from aplastic anaemia, is discussed. Sternal puncture is particularly valuable, since true megaloblasts do not occur in the marrow in aplastic anaemia.

5. The clinical and pathological findings confirm our previous suggestion that achrestic anaemia is due to a failure to utilize, or to mobilize from the tissue stores, the antipernicious anaemia liver principle.

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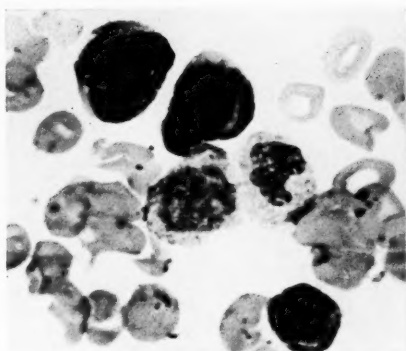


FIG. 1. Case 2. Megaloblasts A and metamyelocytes (below)

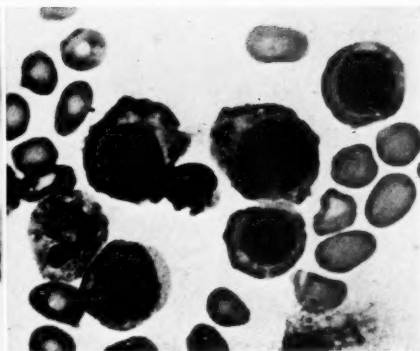


FIG. 2. Case 3. Megaloblast B and (lower left) a polymorphonuclear and a myelocyte

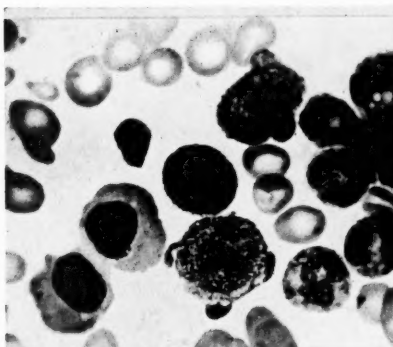


FIG. 3. Case 4. Lower left—megaloblast B, lower centre—pro-erythroblast, right—metamyelocytes and early polymorphonuclears

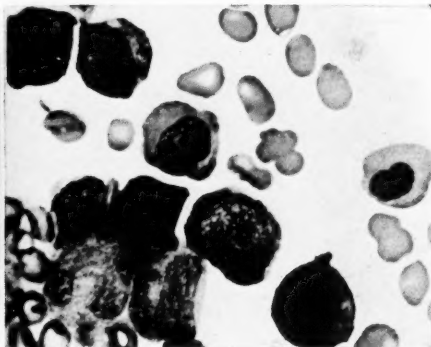


FIG. 4. Case 5. Before liver treatment. Megaloblasts in various stages and typical large metamyelocytes

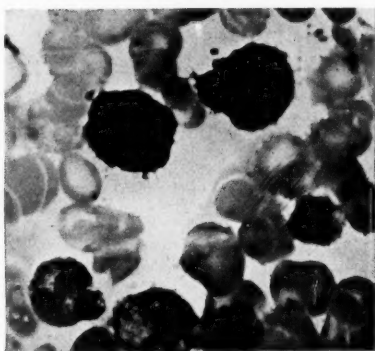


FIG. 5. Case 5. After liver treatment. Normoblasts A

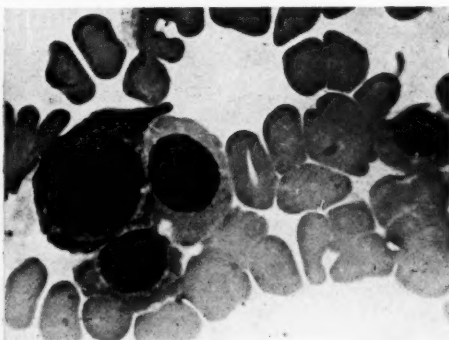
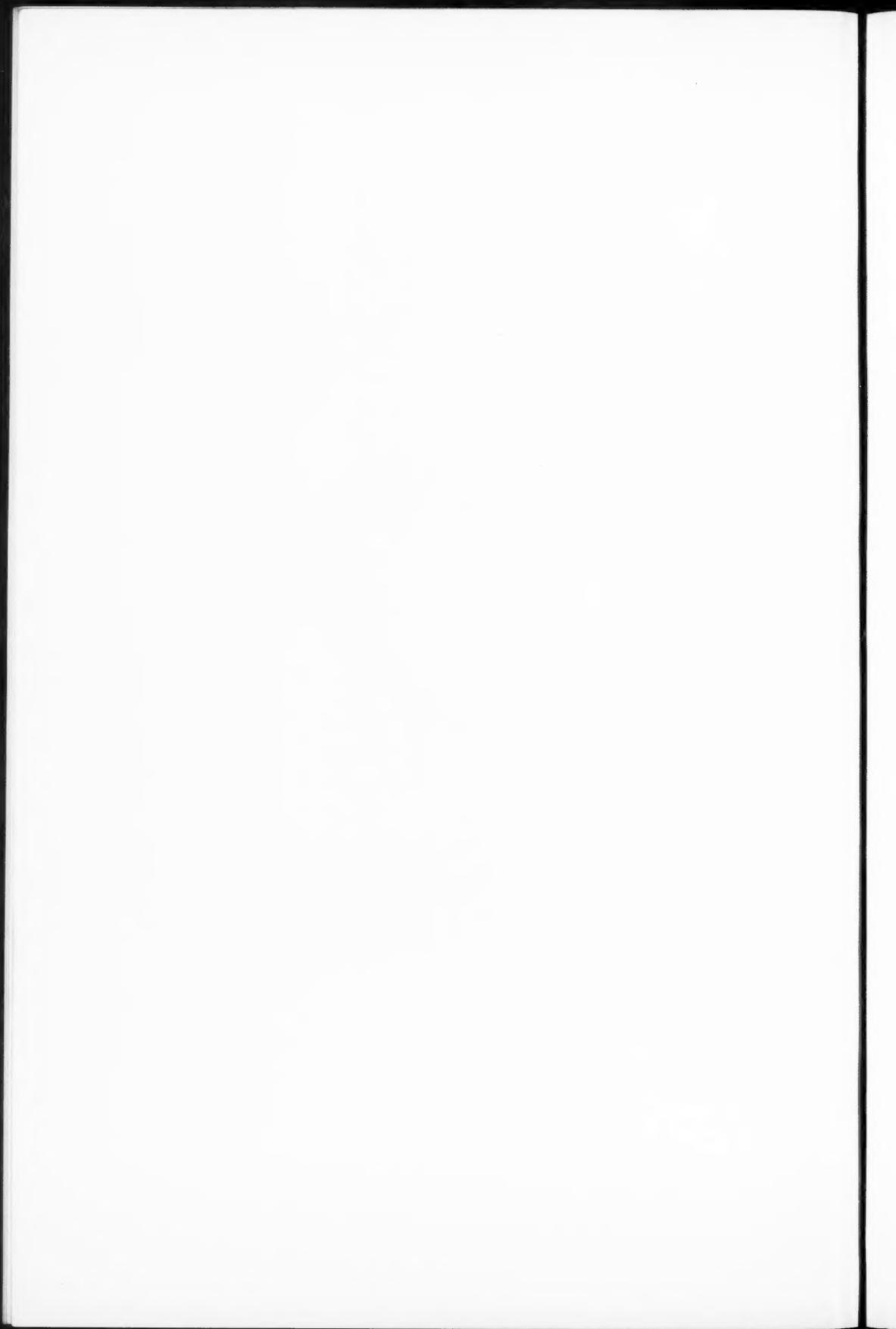


FIG. 6. Case 6. Haemocytoblast and two megaloblasts B

Photomicrographs from sternal marrow smears. Stain, Jenner-Giemsa. Magnification  $\times 1300$



ALEUKAEMIC LEUKAEMIA<sup>1</sup>

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With Plates 6 to 9

SINCE the beginning of this century it has been known that leukaemia may not manifest itself by any notable increase in the number of leucocytes in the blood. Such a leukaemia is commonly described as aleukaemic, though a minority of authors have used the term only when the types as well as the numbers of leucocytes in the blood have been normal. In this paper the term aleukaemic leukaemia is used in its wider sense, that of a leukaemia without gross leucocytosis. An attempt has been made to classify the various types of disease described, working on the basis of a study of the literature, and of cases of leukaemia seen in the Courtauld Research Unit of the Middlesex Hospital during the past three years.

The leukaemias are commonly differentiated into the acute, chronic myeloid, and chronic lymphatic types, in all of which there may at some time be an aleukaemic phase. The same differentiation is applicable to the leukaemias which never depart from an aleukaemic course, but the diagnosis between these and other blood diseases with a low leucocyte count presents special problems.

*The diagnosis of aleukaemic leukaemia.* The difficulty in diagnosis of aleukaemic leukaemia has always attracted attention. Full and frequent blood counts are essential, for they will suggest the diagnosis even when they do not establish it. When the blood picture is not that of a frank leukaemia the diagnosis can be made only by sternal biopsy. Marrow is most simply obtained by sternal puncture, and smears made in this way are usually diagnostic in leukaemia and do not differ, whether the blood picture is aleukaemic or not (Hynes, 1939). When marrow cannot be obtained by sternal puncture, either through faulty technique or because the marrow is aplastic, a specimen of sternal marrow must be removed by trephine and examined histologically. The marrow histology of leukaemia is diagnostic—the affected leucocytes are enormously increased, obliterating the normal structure of the marrow, and leaving only a few scattered foci of the normal haematopoietic elements. Thus by histology such conditions as aplastic anaemia and myelosclerosis are excluded from the diagnosis.

<sup>1</sup> Received December 28, 1939.

*Aleukaemic Acute Leukaemia*

In the usual types of acute leukaemia the leucocyte count is from 20,000 to 40,000 per c.mm., but lower figures are common. Watkins (1933), for example, found that 45 per cent. of the cases of acute leukaemia seen at the Mayo Clinic in four years had leucocyte counts persistently under

TABLE I

*Blood Counts of Case 1*

Date.	Hb. (Haldane) %	R. B. C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Myelocytes %	Myeloblasts %	Lymphocytes %	Monocytes %	Normoblasts %	Erythroblasts %	Megaloblasts %	Platelets.
11.11.36	54	3.3	9,000	1.5	—	3	74.5	20	1	0.5	—	—	—
14.11.36	46	2.1	9,000	1.5	0.5	3	79	16	—	—	—	—	—
16.11.36	53	3.0	7,500	1	—	3	81	15	—	—	—	0.5	—
18.11.36	54	3.1	10,000	1	2.5	3	75	17	1.5	—	—	0.5	—
20.11.36	52	2.7	8,500	2	1.5	5	78	13	0.5	1	—	—	—
24.11.36	41	2.3	5,300	2	1	3.5	73	20	0.5	2	—	—	—
27.11.36	40	2.0	7,000	1	—	5	75	19	—	2.5	1	0.5	—
30.11.36	33	1.6	11,000	1	—	1.5	82	15.5	—	1.5	—	—	—
2.12.36	26	1.3	6,000	0.5	0.5	3	80	16	—	1.5	—	—	—
4.12.36	23	1.2	11,000	—	—	2	87	11	—	0.5	—	—	—

A very few giant forms only were seen in the films.

TABLE II

*Marrow Differential Counts in Cases of Leucopenic Acute Leukaemia*

Case.	Polymorphus %	Metamyelocytes %	Myelocytes %	Premyelocytes %	Myeloblasts %	Lymphocytes %	Lymphoblasts %	Plasma cells %	Monocytes %	Premonocytes %	Normoblasts %	Erythroblasts %	Megaloblasts %
1	1.5	—	0.5	36	55	7	—	—	—	—	—	—	—
2	—	—	0.5	3.5	70	*23	—	2	—	—	0.5	0.5	—
3	1.0	0.5	0.5	27	40	*16	—	—	4	—	6	5	—
4	4.0	0.5	0.5	1	66	27.5	—	—	—	—	—	0.5	—
5	13.5	2.5	2.5	0.5	—	28	35	—	—	—	13	4.5	0.5
6	2.5	1.5	2	5	1	66	14	—	—	—	1	3.5	2.5
7	0.2	0.1	0.1	0.1	†	2	—	—	—	93.5	2.4	1.2	0.4

\* ?Micromyeloblasts.

† Myeloblasts were indistinguishable from the earliest premonocytes or monoblasts.

10,000 per c.mm., and various authors have reported persistent leucopenia in from a third to a quarter of their cases of acute leukaemia in children. Numerous papers give short series of this type of case. During the past three years 23 cases of acute leukaemia have been personally investigated in the Middlesex Hospital, and seven of these, which are described below, had a normal or subnormal leucocyte count throughout their course.



*Case 1. Leucopenic acute myeloid leukaemia.* B. O., a girl aged 21 years, had suffered for a month from sore throat, swelling and bleeding of the gums, and fever. The gums were grossly swollen (Plate 6, Fig. 1), and there were shallow ulcers of the buccal and pharyngeal mucosa. Neither spleen, liver, nor lymph nodes were palpable. Blood counts (Table I) showed

TABLE III  
*Blood Counts of Case 2*

Date.	Hb. (Haldane) %	R. B. C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Myelocytes %	Myeloblasts %	Lymphocytes %	Monocytes %	Plasma cells %	Platelets per c.mm.
2.2.38	28	1.3	2,000	26	1	11	55	7	—	5,600
3.2.38	28	1.2	1,300	22	1	21	47	6	3	none seen
4.2.38	38	1.5	2,100	26	1	29	40	3	1	"
5.2.38	38	1.7	2,800	15	—	29	50	4	2	"
7.2.38	39	1.9	2,300	18	—	33	46	2	1	"
8.2.38	39	1.9	2,000	6	3	50	33	5	3	"
9.2.38	35	1.5	2,600	6	2	57	30	5	—	"

TABLE IV  
*Blood Counts of Case 3*

Date.	Hb. (Haldane) %	R. B. C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Myeloblasts %	Lymphocytes %	Monocytes %	Normoblasts %	Erythroblasts %	Platelets.
24.1.38	29	1.2	1,600	16	31	40	12	2	2	Deficient
25.1.38	53	2.6	1,200	15	41	34	10	1	5	"

a normal total leucocyte count, but the majority of the cells were myeloblasts. Sternal biopsy confirmed the diagnosis of acute leukaemia; the differential count of the marrow smears is given in Table II, and Plate 6, Fig. 3, shows the complete replacement of the marrow by very primitive myeloid cells. The necropsy, after three months' illness, was typical of acute leukaemia.

*Case 2. Leucopenic acute myeloid leukaemia.* M. W., a girl aged 19 years, had been ill for five weeks with fever, weakness, epistaxis, and bleeding from the gums. She was very pale, the gums were swollen, and there were many haemorrhages in the fundi, but neither spleen, liver, nor lymph nodes were palpable. Blood counts (Table III) showed severe anaemia, leucopenia, and many myeloblasts. The bone-marrow, obtained by sternal puncture and trephine, was diagnostic of acute leukaemia (Table II; Plate 7, Fig. 4). Death occurred within a week, but at necropsy there was little macroscopic evidence of leukaemia. Histological sections, however, showed infiltration of the spleen, liver, and lymph nodes with myeloblasts and early myelocytes.

*Case 3. Leucopenic acute myeloid leukaemia.* E. W., a woman aged 57 years, had a history of increasing pallor and weakness of three months' duration. She was prostrate and had extensive bed-sores, the tip of the spleen was palpable, but neither liver nor lymph nodes were enlarged. Blood counts (Table IV) and sternal puncture (Table II) were diagnostic of acute leukaemia. The patient died three days after admission, but autopsy was refused.

TABLE V

*Blood Counts of Case 4*

Only a proportion of the counts done is given.

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Myeloblasts %	Lymphocytes %	Monocytes %	Normoblasts %	Platelets.
23.8.38	44	1.8	2,000	17	—	—	6	1.5	74	1.5	—	Very scanty throughout
30.8.38	50	2.2	1,000	22	1	—	6	3	67	1	—	
13.9.38	75	3.4	2,300	10	1	—	—	—	84	5	—	
20.9.38	63	—	2,250	24	2	—	6	9	56	2	1	
27.9.38	38	—	2,000	14.5	3	1	8	13	57.5	3	—	
4.10.38	49	2.4	1,500	2	0.5	—	0.5	13	82	2	—	
10.10.38	43	2.1	3,500	3	—	—	1	54	40	2	—	

*Case 4. Leucopenic acute myeloid leukaemia.* F. W., a man aged 57 years, had complained of lassitude and breathlessness on exertion for eight months. Pallor and a barely palpable spleen were the only physical signs. Blood counts (Table V) showed an anaemia with a high colour index, but the mean corpuscular volume was normal (78 cu.  $\mu$ ). There was leucopenia with marked neutropenia, and a few primitive myeloid cells were present; platelets were very scanty. Sternal puncture twice yielded a fluid containing very few cells, most of which were myeloblasts (Table II). The tentative diagnosis of acute leukaemia was confirmed by necropsy two months later; the bone-marrow was packed with myeloblasts and the organs similarly infiltrated.

*Case 5. Leucopenic acute lymphatic leukaemia.* L. W., a man aged 21 years, had noticed multiple enlargement of lymph nodes for three months. There was no anaemia, but marked leucopenia with a few lymphoblasts (Table VI). Sternal puncture was diagnostic of acute lymphatic leukaemia (Table II). Two small doses of deep X-rays to the neck produced an almost complete neutropenia which persisted for a month (Table VI). The haemoglobin fell progressively to 58 per cent., but the leucocyte count never rose above 3,000 per c.mm. The patient died four months after admission to hospital, but no autopsy was obtained.

*Case 6. Leucopenic acute lymphatic leukaemia.* E. S., a girl aged 17 years had had fever for two months without physical signs. Blood counts (Table VII) showed severe anaemia and leucopenia, with some abnormal lymphocytes not primitive enough to be called lymphoblasts. The diagnosis of acute lymphatic leukaemia was made by sternal biopsy (Table II; Plate 7, Fig. 5), the marrow being completely replaced by primitive lymphoid cells. Later the leucocyte count once rose to 80,000 per c.mm. with 46 per cent.

of lymphoblasts, and though the total count rapidly fell again the primitive cells persisted. The patient died fourteen weeks after the onset of her illness, and a necropsy was typical of leukaemia. In this case there was a considerable leucocytosis on one occasion only, but it is included to illustrate the close connexion between the two forms of acute leukaemia.

TABLE VI

*Blood Counts of Case 5*

Only a proportion of the counts done is given.

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Lymphocytes %	Lymphoblasts %	Monocytes %	Normoblasts %	Platelets.
28.10.38	90	5.0	2,500	50	13	1	33	—	3	—	Normal in films
4.11.38	92	4.6	1,400	36	30	2	23	6	3	—	
10.11.38	85	—	1,300	1	26	—	51	14	2	—	
17.11.38	84	—	800	5	—	—	53	34	2	0.5	
23.11.38	66	2.8	600	16	1	—	47	36	—	—	
2.12.38	64	2.6	1,500	31	3	—	41	25	—	—	
10.12.38	70	3.5	2,000	46	9	1	34	10	—	—	
20.12.38	58	2.7	2,600	59	15	0.5	20	5	0.5	—	
28.12.38	58	3.1	3,000	55	18	—	24	3	—	—	
10.1.39	58	3.1	900	44	5	—	46	4	1	—	Scanty

TABLE VII

*Blood Counts of Case 6*

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Lymphocytes %	Lymphoblasts %	Monocytes %	Nucleated R.B.C.	Platelets per c.mm.
16.11.35	42	3.0	1,700	15	83	—	2	—	—
18.11.35	36	1.6	725	39	56	—	5	—	20,000
20.11.35	90	4.6	850	54	42	—	4	—	—
25.11.35	82	4.2	2,250	30	69	—	1	—	—
2.12.35	—	3.0	2,400	35	62	—	3	—	—
9.12.35	86	4.3	3,750	34	65	—	1	—	—
17.12.35	90	4.5	80,000	2	52	46	—	—	Very few
27.12.35	55	3.4	6,000	17	50	32	1	—	Very scanty
2.1.36	46	2.1	9,500	5	63	30	2	0.5	—

*Case 7. Leucopenic acute monocytic leukaemia.* I. K., a woman aged 33 years, had noticed a hard lump over the right nasal bone for two weeks. X-rays showed no bony abnormality, and biopsy was refused, so the tumour was treated by radium as a probable neoplasm. A dose of 2,000 mg.-hours from the Gramme unit quickly caused so much local oedema that the treatment was stopped. The oedema subsided within a week, but the neck then began to swell and ulcers appeared in the mouth. The patient did not attend the hospital again until she was admitted six weeks after her first visit. She was prostrate, very pale, with extensive swelling of the neck, an ulcerated

mouth, and hypertrophic gums. The cervical lymph nodes alone were enlarged, but neither spleen nor liver was palpable. Blood counts (Table VIII) revealed acute leukaemia, and supravital staining showed the primitive cells to be early monocytes. The diagnosis was confirmed by sternal biopsy (Table II; Plate 7, Fig. 6) and by necropsy four months later.

TABLE VIII

*Blood Counts of Case 7*

Only a proportion of the blood counts done is given. Most of the cells recorded as monocytes were of a very primitive type, large, with nucleoli, and many coarse azurophil granules.

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Myeloblasts %	Lymphocytes %	Monocytes %	Normoblasts %	Erythroblasts %	Platelets.
18.10.37	56	2.2	6,000	4	—	—	—	2	34	59	1.5	0.5	Deficient throughout
20.10.37	52	2.3	1,500	6	1	0.5	—	1	76.5	15	1	—	
27.10.37	38	1.9	2,500	11.5	0.5	—	—	3	58	27	—	—	
3.11.37	40	1.8	4,000	9	0.5	0.5	—	2	55	36	1	0.5	
6.11.37	40	1.6	5,500	11	—	—	—	2	42	45	1.5	—	
8.11.37	60	2.8	1,800	15	0.5	—	0.5	1	38	45	3	0.5	
11.11.37	58	2.6	5,000	8	0.5	—	0.5	1	48	42	0.5	—	
19.11.37	58	2.4	1,700	10	—	—	0.5	3	57.5	29	1	0.5	
24.11.37	55	2.2	2,200	10	0.5	—	—	0.5	65	24	—	—	
1.12.37	48	1.2	3,500	9	—	—	0.5	1.5	38	51	0.5	—	
7.12.37	39	2.0	1,900	16	0.5	0.5	—	1	54	28	—	—	
13.12.37	42	1.8	1,800	19	—	—	—	1	55	25	1.5	0.5	
17.12.37	38	1.6	1,000	35	0.5	—	0.5	2	35	27	0.5	0.5	

These cases and the cases of 'acute aleukaemic leukaemia' in the literature differ neither clinically nor pathologically from other acute leukaemias. It is not justifiable to classify them as a separate type of acute leukaemia, so that it is better to call them leucopenic rather than aleukaemic. Their diagnosis is, however, difficult enough to merit consideration.

*The features of acute leukaemia.* The clinical and haematological features of acute leukaemia are usually quite definite. The patient is very pale, and purpura and haemorrhages from the mucosae are common. Often neither spleen, liver, nor lymph nodes are palpable, though at autopsy they are always infiltrated by leukaemic cells. Ulceration and sepsis in the mouth is common, and often there is a peculiar condition of the gums; they are swollen and almost bury the teeth, their colour is pale bluish-purple, and they are commonly bleeding. In adults the anaemia is usually macrocytic, the red cells vary greatly in size and shape, and many are polychromatic. In children the anaemia is more commonly microcytic and hypochromic. Primitive leucocytes are almost always present in the blood, but their number varies greatly from case to case. Supravital staining may be necessary to determine the nature of the primitive cells. Extreme thrombocytopenia is almost invariable, and is associated with purpura and haemorrhages.

*Differential diagnosis.* In *aplastic anaemia*, as in acute leukaemia, there is fever, severe anaemia, purpura, and often agranulocytosis. In aplastic anaemia the blood may contain a few myelocytes and myeloblasts, up to 5 per cent. of the total leucocyte count (Rosenthal, 1931), so that the blood picture is not clearly distinct from that of cases of acute leukaemia in which primitive cells are scanty. The bone-marrow in aplastic anaemia is hypoplastic, whereas in leukaemia it is very cellular, so that sternal biopsy differentiates between the two. Hypoplasia of the marrow can be demonstrated only by histological examination of trephined specimens, for failure to obtain marrow by sternal puncture may be due to faulty technique. Aplastic anaemia may rarely be associated with an active or even a very hyperplastic marrow (Rhoads and Miller, 1938), the only distinction from acute leukaemia being that the organs are not infiltrated with primitive leucocytes. Here the differential diagnosis depends on necropsy.

Often the predominating features of acute leukaemia are those of *agranulocytosis*, fever, and ulceration of the mouth and throat, but in agranulocytosis there is neither anaemia nor thrombocytopenia and haemorrhages. This distinction may not be clear when agranulocytosis is due to drugs such as gold or arsenic, which may affect the leucocytes, red cells, or platelets separately or in any combination. Acute leukaemia may begin by exactly simulating agranulocytosis; Jackson and Parker (1935) described three patients with agranulocytosis who were apparently cured by pentnucleotide, but later died of acute leukaemia. In the early stages of agranulocytosis the cellularity of the marrow is normal, but myeloblasts replace the myelocytes and polymorphs. The myeloblasts gradually disappear, until after eight to ten days a few lymphocytes and plasma cells are the only leucocytes in the marrow. When the blood picture is improving the marrow is hyperplastic and crowded with myelocytes and young polymorphs (Jackson and Parker, 1935).

O'Donaghue and Witts (1932) first emphasized the similarity between acute leukaemia and Lederer's anaemia in children. Even the thrombocytopenic syndrome may occur in Lederer's anaemia, but a blood transfusion is an immediate cure for this disease. Von Jaksch's anaemia is distinguished from acute leukaemia by its long course and final recovery. Lastly, in overwhelming infections the blood picture has in rare cases been identical with that of acute leukaemia.

*Treatment.* There is no effective treatment for acute leukaemia. Deep X-ray therapy may relieve the pressure symptoms of a leukaemic mediastinal tumour (Cooke, 1933), but it relieves no other symptoms. Even small doses may rapidly increase the neutropenia and anaemia (as in Case 5). Blood transfusion may effect a temporary improvement, and usually checks haemorrhage, but the blood given is destroyed very quickly. In the writer's experience blood transfusion has been harmful as often as beneficial, but it should be tried at least once in case the true diagnosis may be Lederer's anaemia.

*Aleukaemic Chronic Myeloid Leukaemia*

Aleukaemic phases of chronic myeloid leukaemia are common. After successful X-ray treatment the blood count may remain normal or almost normal for months, the leucocyte count may fall during intermittent febrile complications, and rarely there may be a spontaneous remission. In aleukaemic chronic myeloid leukaemia, however, the leucocyte count is never raised.

When cases of leucopenic acute myeloid leukaemia have lived longer than is usual they have sometimes been described by this title or its synonym 'aleukaemic myelosis'. Mettier and Purviance (1937), for example, described five cases of 'aleukaemic myelosis without splenomegaly', but these had all the features of leucopenic acute myeloid leukaemia except for a protracted course up to eleven months.

*Aleukaemic myelosis.* The very chronic forms of aleukaemic myeloid leukaemia merge with the syndrome often described as 'aleukaemic myelosis'. In this syndrome the patient, who is usually from 40 to 60 years of age, has a very large spleen and usually an enlarged liver. There is a variable degree of anaemia without leucocytosis, and nucleated red cells are at least as numerous in the blood as primitive white cells. The patient may die within a few months, or may live for ten or twenty years.

Arneth (1901) called this syndrome leukanaemia, to indicate the resemblance of the anaemia to pernicious anaemia, and of the leucocyte count to leukaemia. This word has appeared in the text-books with a variety of meanings until very recently, though it disappeared from scientific medical literature twenty years ago. In 1905 Hirschfeld suggested that the syndrome represented an atypical myeloid leukaemia, and in 1914 he first called it 'aleukaemic myelosis' in contrast with 'leukaemic myelosis', the ordinary chronic myeloid leukaemia. This term was generally accepted, but it was gradually realized that leukaemia was not the only cause of the syndrome. Emil-Weil has studied this syndrome since 1902, and now regards it as 'un syndrome toxi-infectieux d'étiologies multiples'. He believes that the leukaemia is usually a terminal complication of a long-standing infection, but that a few cases are leukaemic from the beginning. In 1933 Chapman, and Stephens and Bredeck, described myelosclerosis as a cause of this syndrome. The differential diagnosis between aleukaemic leukaemia and myelosclerosis is very difficult, and has rarely been attempted, or even recognized, in the cases of 'aleukaemic myelosis' in the literature.

The syndrome occurs equally in either sex and at all ages, though it is commonest from 40 to 60 years. The patient complains first either of the enormous spleen or of symptoms due to anaemia, but the history of the illness never seems long enough for the spleen to have grown so large. The patient wastes greatly as the disease progresses. The liver is usually enlarged, though less so than the spleen, but enlarged lymph nodes are never found. The thrombocytopenic syndrome is rare. The anaemia may be slight or extreme, it is usually macrocytic, sometimes normocytic, and



rarely microcytic. The red cells vary in shape and size and many are polychromatic. The leucocyte count is normal or slightly raised, myelocytes and a few myeloblasts are present, but normoblasts are more numerous. The patient usually lives from five to ten years after the diagnosis, but many of the reported cases have been killed by splenectomy.

TABLE IX  
*Blood Counts of Case 8*

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Myeloblasts %	Lymphocytes %	Monocytes %	Normoblasts %	Platelets.
7.1.36	88	4.7	11,000	62	—	1	15	2	12	5	0.3	Appear increased
13.1.36	80	4.0	15,000	77	—	—	8	1	10	4	—	"
3.2.36	80	3.8	9,000	73	1	1	8	—	10	7	0.5	Marked increase
19.2.36	70	3.5	9,000	80	3	—	5	—	10	2	—	—
28.3.38	85	4.6	13,000	73	—	1	13	2	8	3	1.0	Normal
15.7.38	89	4.3	12,000	63	0.5	0.5	10	4	17	5	2	"
21.10.38	90	4.4	9,000	66	—	1	13	2	14	4	—	"

TABLE X  
*Bone-marrow Differential Count of Case 8*

	Neutrophil.	Eosinophil.	Basophil.
Polymorphs	33.5	0.5	—
Metamyelocytes	10	—	—
Myelocytes	13	1	—
Premyelocytes	4.5	—	—
Myeloblasts	3.0	—	—
Lymphocytes	1	—	—
Monocytes	—	—	—
Normoblasts	18	—	—
Erythroblasts	12.5	—	—
Megaloblasts	3	—	—

*Case 8. Aleukaemic chronic myeloid leukaemia.* A. P., a woman aged 58 years, had had good health until an attack of shingles one week before admission to hospital. The spleen was enlarged down to the umbilicus, and the liver extended  $2\frac{1}{2}$  in. below the costal margin, but no lymph nodes were palpable. Blood counts (Table IX) showed slight anaemia and up to 15 per cent. of myelocytes in 9,000 to 15,000 leucocytes per c.mm.; an occasional nucleated red cell was seen. Controlled X-rays of the long bones showed no abnormality. Sternal biopsy (Table X; Plate 7, Fig. 7) revealed marked hyperplasia of both myeloid and erythroblastic elements of the marrow, a finding compatible with either chronic myeloid leukaemia or myelosclerosis.

*Case 9. Myelosclerosis.* M. G., a woman aged 80 years, had had three years' symptoms of anaemia. She was very pale, the spleen extended  $3\frac{1}{2}$  in. below the costal margin, and the liver was just palpable, but no enlarged lymph nodes were felt. Blood counts (Table XI) showed extreme anaemia, a few myelocytes, and many nucleated red cells. Sternal puncture yielded fluid identical with the peripheral blood (Table XII). The patient died

TABLE XI

*Blood Counts of Case 9*

Only a proportion of the counts done is given.

Reticulocytes varied from 2 to 22 per cent.; there was macrocytosis, anisocytosis, and hypochromia; the fragility of the red cells was normal.

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Myeloblasts %	Lymphocytes %	Monocytes %	Normoblasts %	Erythroblasts %	Megaloblasts %	Platelets.
12.2.38	32	1.6	10,500	57	2.5	0.5	15	—	21	4	85	4	1	Scanty
18.2.38	21	1.1	5,700	77	—	—	7	—	32	4	124	10	1	"
21.2.38	68	3.4	3,400	76	2	—	2	—	13	7	110	9	1	"
23.2.38	58	2.7	2,900	67	9	—	9	—	13	2	100	12	1	"
26.2.38	34	1.8	2,500	65	4	2	5	6	18	6	76	7	—	"
2.3.38	32	1.6	8,000	55	4	0.5	10	0.5	15	15	50	4	—	"
8.3.38	28	1.3	4,600	76	0.5	0.5	2	—	16	5	65	6	—	"
12.3.38	24	1.2	6,000	68	1	3	3	—	14	11	60	8	—	"

TABLE XII

*Marrow Differential Counts in Cases of Myelosclerosis*

Case.	Polymorphs %	Metamyelocytes %	Myelocytes %	Prenyelocytes %	Myeloblasts %	Lymphocytes %	Monocytes %	Normoblasts %	Erythroblasts %	Megaloblasts %
9	39	1.5	3	—	—	3	1.5	44	7	1
10	1.5	0.5	0.25	0.25	1.0	92	1.5	1.5	1.5	—

TABLE XIII

*Blood Counts of Case 10*

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Lymphocytes %	Monocytes %	Normoblasts %	Erythroblasts %	Platelets.
31.3.38	33	1.8	2,000	29	4	2	—	63	2	5	2	Scanty
5.4.38	32	1.6	1,000	36	2	1	—	57	4	5	1	"
12.4.38	40	2.0	500	50	1	—	1	46	2	6	4	"
16.4.38	38	2.2	1,800	31	1	—	—	62	6	2	3	"
20.4.38	38	2.0	1,800	29	1.5	1	0.5	66	2	2	1	"
27.4.38	42	2.1	1,500	13	2	—	—	80	5	2	4	"
2.5.38	37	1.9	1,000	29	1	1	—	68	1	3	1	"
5.5.38	47	2.3	1,200	33	1	—	—	64	2	6	4	"
16.7.38	44	1.9	800	36	—	—	—	63	1	1	1	"
10.10.38	37	1.8	1,200	43	10	—	—	42	4	1	—	"
15.12.38	17	0.65	800	15	—	—	—	81	4	1	—	Very scanty
27.1.39	70	3.5	2,100	32	1	—	—	64	3	—	—	Normal

after a month, and necropsy was performed. The spleen was firm, deep red, and contained many infarcts; the liver was enlarged and pale; and a few enlarged lymph nodes were found in the neck and mediastinum. The marrow of the bones examined (femur, sternum, lumbar vertebrae, and skull) was deep red and in the long bones filled the central canal. Histologically the marrow in all the bones was replaced by vascular and engorged fibrous tissue, there being only scattered islands of haematopoiesis (Plate 8, Fig. 8). The spleen, liver, and lymph nodes were infiltrated with nucleated red cells and an occasional myelocyte, and one of the glands contained tuberculous giant-cell systems.

*Case 10. Myelosclerosis.* C. J., a man aged 65 years, had noticed palpitation and breathlessness on exertion for nine weeks. He was very pale, the spleen extended to the umbilicus, and the liver extended  $1\frac{1}{2}$  in. below the costal margin; no lymph nodes were palpable. Blood counts (Table XIII) showed a severe macrocytic anaemia with 3.5 per cent. of reticulocytes, and marked leucopenia. Controlled X-rays showed sclerotic changes in the long bones. Marrow smears obtained by sternal puncture and trephine gave the same differential counts (Table XII), and sections showed the marrow to be completely replaced by vascular fibrous tissue (Plate 8, Fig. 9). The patient is still alive, having had repeated blood transfusions.

The syndrome illustrated by these three cases may be caused either by chronic myeloid leukaemia or by myelosclerosis. Myeloid metaplasia of the organs is common to both, but the pathology of the bone-marrow separates them. In chronic myeloid leukaemia the normal marrow structure is replaced by masses of primitive myeloid cells, in myelosclerosis it is replaced by fibrous tissue. Very rarely a case of 'aleukaemic myelosis' has terminated as chronic myeloid leukaemia with a high leucocyte count; Pinkerton (1929) described one such case. It has been suggested that myelosclerosis may supervene on chronic myeloid leukaemia, but Vaughan (1936) believes that all such cases should be classified as myelosclerosis.

Myelosclerosis has probably been the true diagnosis of many of the reported cases of 'aleukaemic myelosis'. Often some bones are not affected by the fibrosis, but show instead a marked myeloid hyperplasia, so that neither sternal biopsy nor a limited post-mortem examination necessarily separates the disease from aleukaemic leukaemia. Many authors (e.g. Hickling, 1937) have not thought it necessary to distinguish between leukaemia and myelosclerosis as causes of this syndrome.

In about half the cases of myelosclerosis X-rays of the long bones show slight patchy increases in density which are diagnostic. The changes can be certainly recognized only if a similar normal limb is simultaneously X-rayed on the same plate. The control subject must be of the same sex as the patient, and of nearly the same age and build. If the X-ray is negative the diagnosis can be made only by sternal biopsy with the trephine, and, as shown above, even this method cannot exclude myelosclerosis.

In some cases of 'aleukaemic myelosis' the spleen has contained many giant cells of the bone-marrow type; such cases have been called 'megakaryocytic myelosis'. A study of the literature suggests that this syndrome is commonly due to myelosclerosis, and less often to aleukaemic chronic

myeloid leukaemia. Six of the seven reported cases in which necropsy was performed had active tuberculosis, and the French authors believe that this disease is at least a partial cause of the syndrome. English authors ascribe the association to coincidence.

*Differential diagnosis.* In addition to the syndromes described above, a few other diseases may simulate chronic myeloid leukaemia. Albers-Schönberg's disease is recognized by the early age of onset, the family history, and the very typical radiological changes in the bones. Leuco-erythroblastic anaemia is common in secondary carcinomatosis of the bone-marrow, and an associated splenomegaly has rarely been reported (Martin, Déchaume, and Ben-Rais, 1927). Myeloid metaplasia of the spleen without enlargement is common and may be widespread through the body (Turnbull, 1936). An X-ray of the skeleton may establish the diagnosis, or the radiograms may be normal. The more chronic cases of Lederer's anaemia may cause difficulty, but they may be recognized by their dramatic response to blood transfusion. The spleen in pernicious anaemia may be very large, and in remission the blood contains many primitive red and white cells, but the mean corpuscular volume is much larger than in other anaemias, and the disease responds to liver therapy. Splenic anaemia should never be confused with 'aleukaemic myelosis', even apart from its clinical features. The anaemia is always hypochromic with a leucopenia, and though the blood occasionally contains primitive red cells, primitive leucocytes are never found (Chaney, 1923).

#### *Aleukaemic Chronic Lymphatic Leukaemia*

Aleukaemic chronic lymphatic leukaemia has rarely been described. King (1917) reported two cases in adults, and Spigel (1938) described a child with leucopenic lymphoblastic leukaemia still alive 2½ years after the onset. Of the 16 cases of chronic lymphatic leukaemia personally investigated during the past three years, four have had a leucopenia throughout their course.

*Case. 11. Aleukaemic chronic lymphatic leukaemia.* M. S., a woman aged 52 years, was known to have had an enlarged spleen for eight months before her admission to hospital. She was suffering from shortness of breath, loss of weight, and increasing girth. She was very pale, the spleen extended an inch below the umbilicus, and the liver extended half an inch below the costal margin, but no lymph nodes were palpable. Blood counts (Table XIV) suggested a diagnosis of aleukaemic lymphatic leukaemia, which was confirmed by sternal biopsy (Table XV; Plate 8, Fig. 10). She was treated by deep X-rays to the chest and by blood transfusion; her spleen became much smaller and her general condition improved. She relapsed within six months, but a severe neutropenia precluded further radiotherapy, and after two months more she died of cerebral haemorrhage. No autopsy was obtained.

*Case 12. Aleukaemic chronic lymphatic leukaemia.* W. H., a man aged 45 years, had had symptoms of anaemia for several months, and recent epistaxis. There were large lymph nodes in the axillae and groins, but neither spleen nor liver was palpable. The diagnosis of aleukaemic lymphatic leukaemia was suggested by blood counts (Table XVI), and confirmed

TABLE XIV

*Blood Counts of Case 11*

Date.	Hb. (Haldane) %	R. B. C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Lymphocytes %	Lymphoblasts %	Monocytes %	Normoblasts %	Erythroblasts %	Platelets per c.mm.
7.1.36	52	2.5	13,000	16	—	—	—	57	17	10	—	—	250,000
18.1.36	52	2.5	14,000	18	—	—	—	65	7	10	2	—	Normal
29.1.36	50	2.3	20,000	38	1	1	1	48	5	6	0.5	—	"
11.2.36	60	2.5	12,000	39	—	1	—	46	9	5	—	—	"
28.2.36	50	2.1	6,600	44	3	—	—	43	5	5	—	—	"
5.3.36	45	1.9	3,000	45	—	—	—	43	5	7	—	—	"
1.4.36	60	2.9	2,800	54	—	—	—	38	6	2	—	—	"
28.5.36	46	2.2	6,600	49	—	—	—	30	16	5	2	—	"
13.6.36	70	3.3	1,500	—	—	—	—	—	—	—	—	—	"

TABLE XV

*Marrow Differential Counts in Cases of Aleukaemic Chronic Lymphatic Leukaemia*

Case.	Polymorphs %	Metamyelocytes %	Myelocytes %	Premyelocytes %	Myeloblasts %	Lymphocytes %	Lymphoblasts %	Monocytes %	Normoblasts %	Erythroblasts %	Megaloblasts %
11	8.5	4	7	3	2	55	4	—	7	7.5	2
12	2	6	6	6	6	97	1	—	—	—	—
13	10	2	4	1	1	76	1	—	2	2	1
14	6.6	1.6	1.0	0.6	—	84.4	—	0.2	2.6	2.4	0.6

TABLE XVI

*Blood Counts of Case 12*

Date.	Hb. (Haldane) %	R. B. C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Lymphocytes %	Monocytes %	Normoblasts %	Platelets
25.2.36	25	1.0	2,800	16	5	1	74	4	1	Very scanty
28.2.36	25	1.6	2,300	17	4	1	73	5	1	"
3.3.36	24	1.4	—	—	—	—	—	—	—	"
16.3.36	25	1.0	3,600	20	—	1	76	3	0.5	"
28.4.36	23	0.9	3,000	20	3	—	74	3	—	"
25.5.36	18	0.8	2,000	6	—	—	90	4	1	"
10.6.36	15	0.7	2,000	18	—	—	78	4	—	"

by sternal biopsy (Table XV; Plate 8, Fig. 11). The patient was given repeated blood transfusions, but died after nine months. No autopsy was obtained.

TABLE XVII  
*Blood Counts of Case 13*

Date.	Hb. (Haldane) %	R. B. C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Lymphocytes %	Lymphoblasts %	Monocytes %	Normoblasts %
21.1.36	30	1.5	11,500	20	—	2	—	74	—	4	—
29.1.36	32	1.6	8,000	32	1	1	1	60	2	3	—
13.2.36	30	1.5	8,200	29	—	—	—	65	—	6	3
26.2.36	30	1.8	7,000	20	2	—	—	70	—	6	1
2.3.36	50	2.4	8,000	28	—	1	—	65	—	6	—
30.3.36	45	2.4	12,000	31	—	—	1	56	—	12	—
29.4.36	38	2.6	8,100	24	—	—	4	60	1	11	—
2.7.36	20	1.0	9,300	32	—	—	1	65	—	1	—

TABLE XVIII  
*Blood Counts of Case 14*

Only a proportion of the counts done is given.

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Myelocytes %	Lymphocytes %	Lymphoblasts %	Monocytes %	Nucleated R.B.C. %
29.1.37	35	1.9	14,000	36	1	0.5	—	52	—	10.5	0.75
12.2.37	33	1.9	7,000	30	1	1	—	54	—	14	—
22.2.37	35	1.9	6,000	36	2	—	—	52	—	10	—
3.3.37	35	2.0	6,000	40	2	—	—	52	—	6	—
9.3.37	42	2.2	4,600	54	—	1	1	33	3	8	2
20.3.37	33	1.8	4,000	49	1	—	—	43	—	7	—
30.3.37	30	1.6	4,000	62	1	—	—	24	—	13	—
7.4.37	34	1.4	3,000	55	3	1	1	27	—	13	—
12.4.37	36	1.9	4,200	54	1	—	—	41	—	4	—
26.5.37	48	2.1	5,000	55	4	1	—	36	—	4	0.5

*Case 13. Aleukaemic chronic lymphatic leukaemia.* F. P., a man aged 47 years, had noticed increasing pallor and weakness for a year, and had recently had epistaxis. There was multiple lymph node enlargement, but neither spleen nor liver was palpable. Blood counts (Table XVII) showed severe anaemia and a relative lymphocytosis, and the diagnosis was made by sternal biopsy (Table XV; Plate 9, Fig. 12). He was given repeated blood transfusions, but after seven months he had a profuse epistaxis and died. The lymph nodes were then greatly enlarged, and the spleen was just palpable. No necropsy was obtained.

*Case 14. Aleukaemic chronic lymphatic leukaemia.* A. H., a woman aged 57 years, had noticed increasing pallor, breathlessness, and palpitation for two years. There was multiple lymph node enlargement, and the spleen



extended  $2\frac{1}{2}$  in. and the liver  $1\frac{1}{2}$  in. below the costal margin. Blood counts (Table XVIII) showed extreme anaemia, a normal total leucocyte count, and an absolute lymphocytosis. The diagnosis of lymphatic leukaemia was confirmed by sternal biopsy (Table XV; Plate 9, Fig. 13). Very small doses of deep X-rays, controlled by frequent blood counts, were given to the spleen and trunk. The lymph nodes and spleen became much smaller, but

TABLE XIX  
*Blood Counts of Case 15*

Date.	Hb. (Haldane) %	R.B.C. millions per c.mm.	Leucocytes per c.mm.	Neutrophils %	Eosinophils %	Basophils %	Lymphocytes %	Monocytes %	Platelets.
18.12.37	93	—	9,000	70	2	1	16	11	Normal
22.12.37	100	5.6	8,000	72	1.5	0.5	22	4	Normal
10.3.38	40	2.0	1,400	0	—	—	96	4	None seen

the liver enlarged until its lower border reached the umbilicus, and the anaemia did not improve. The patient attended hospital only once more, four months later, by which time the haemoglobin was appreciably higher. Five months later she died at home of empyema.

These cases illustrate the aleukaemic form of chronic lymphatic leukaemia. It is a disease of middle age, with an insidious onset of a year or longer, and characterized by severe anaemia and usually enlargement of the spleen and lymph nodes. The thrombocytopenic syndrome was prominent in three of these four cases. The total leucocyte count is normal, but there is neutropenia, and a relative or absolute lymphocytosis which should suggest the diagnosis. A certain diagnosis can be made only by sternal biopsy. The patient dies within a year, for the severe anaemia, the liability to haemorrhages, and the low resistance to infection associated with the neutropenia, all leave him with a very precarious hold on life.

#### *Lymphosarcoma*

The syndrome described above is quite distinct from lymphosarcoma, in which the white blood-cells and bone-marrow are normal (Hynes, 1939). Cases which seem at first to be typical lymphosarcoma may, however, terminate as acute lymphatic leukaemia after deep X-ray therapy. Kato and Brunschwig (1933) reported two cases and added 15 cases from the literature, and one other is described below.

*Case 15. Lymphosarcoma and acute lymphatic leukaemia.* L. P., a man aged 28 years, was taken ill with sudden swelling of the cervical lymph nodes, fever, and vomiting. An X-ray showed a large tumour in the region of the thymus. Two blood counts (Table XIX) were normal, and a diagnosis of lymphosarcoma was made after biopsy of a lymph node. He was treated by deep X-rays to the chest and cervical nodes, and his condition improved greatly. Three months after the onset he again became acutely ill, and was readmitted to the hospital *in extremis*. A blood count (Table XIX) showed

severe anaemia and leucopenia, and no polymorphs or platelets were seen in the films. Of the lymphocytes, half were normal and half abnormal, but not primitive enough to be called lymphoblasts. At necropsy the thymic tumour and enlarged lymph nodes resembled infiltrating lymphosarcoma, but the liver and bone-marrow were typical of lymphatic leukaemia.

#### Summary

1. The diagnosis of aleukaemic leukaemia is discussed, and is shown to depend on careful and repeated examinations of the blood and on sternal biopsy.

2. 'Acute aleukaemic leukaemia' is a common variant of ordinary acute leukaemia, and does not differ from it, either clinically, pathologically, or haematologically enough to justify a separate name. The differential diagnosis is discussed.

3. Aleukaemic chronic myeloid leukaemia is the cause of some cases of the so-called 'aleukaemic myelosis', though most reported instances of this syndrome have probably been due to myelosclerosis. The differential diagnosis is discussed.

4. A form of aleukaemic chronic lymphatic leukaemia is described, and its relationship with lymphosarcoma is discussed.

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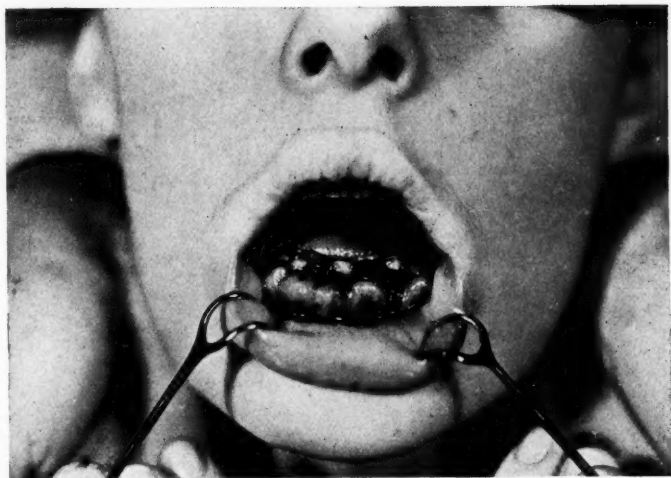


FIG. 1. The gums in Case 1.

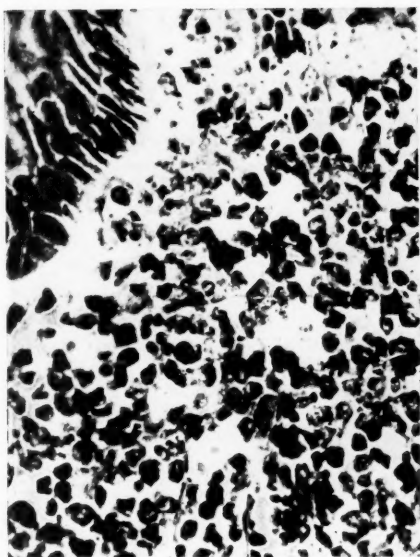


FIG. 2. Section of the gums of Case 1.  
( $\times 640$ )

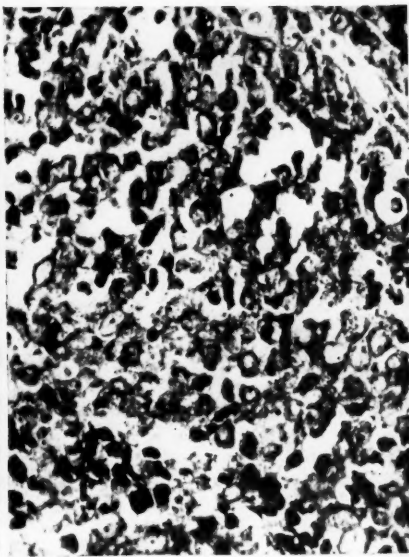


FIG. 3. Bone-marrow of Case 1.  
( $\times 640$ )



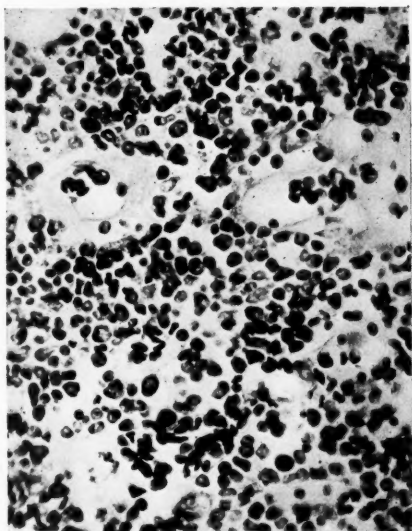


FIG. 4. Bone-marrow of Case 2.  
( $\times 380$ )

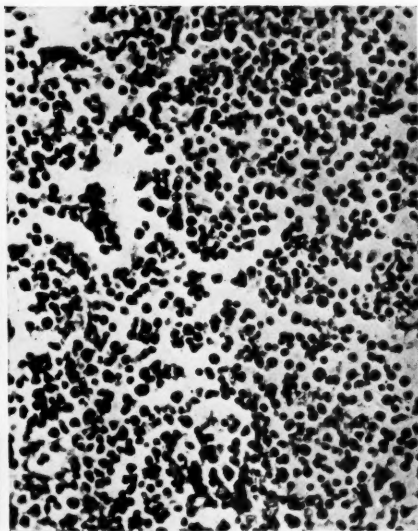


FIG. 5. Bone-marrow of Case 6.  
( $\times 380$ )

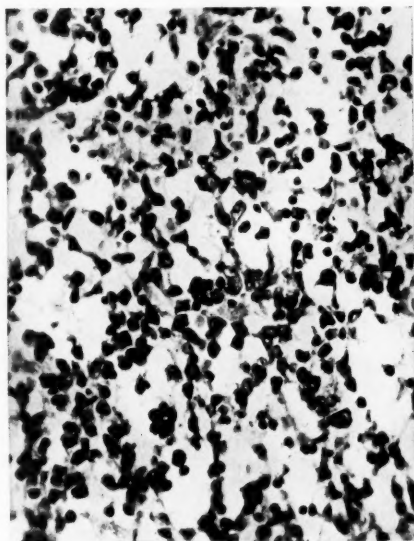


FIG. 6. Bone-marrow of Case 7.  
( $\times 380$ )

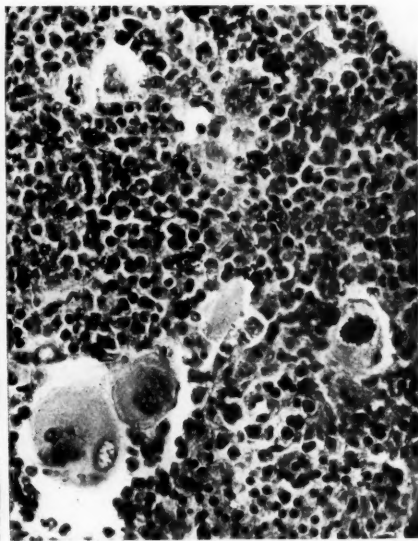


FIG. 7. Bone-marrow of Case 8.  
( $\times 380$ )





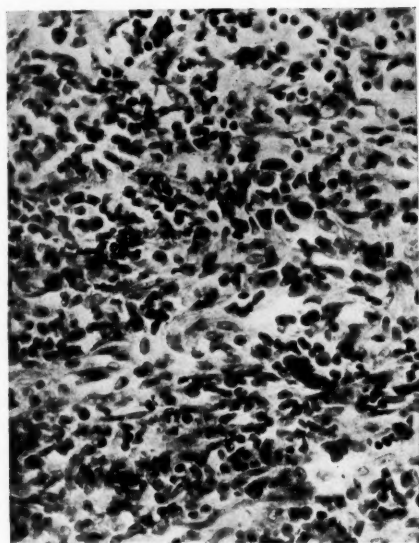


FIG. 8. Bone-marrow of Case 9.  
( $\times 380$ )

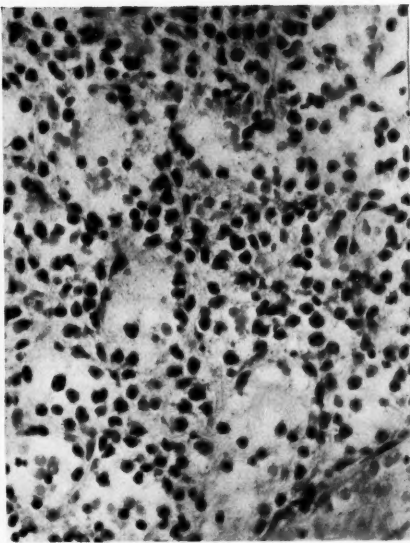


FIG. 9. Bone-marrow of Case 10.  
( $\times 380$ )

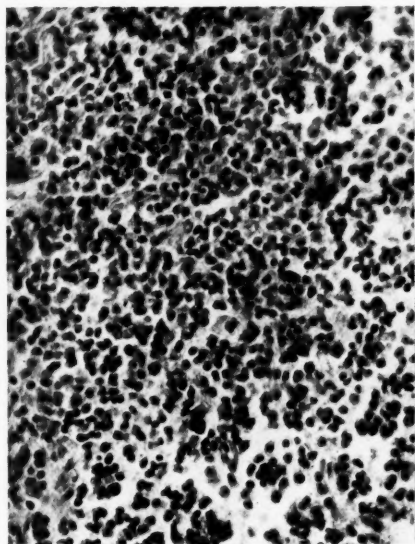


FIG. 10. Bone-marrow of Case 11.  
( $\times 380$ )

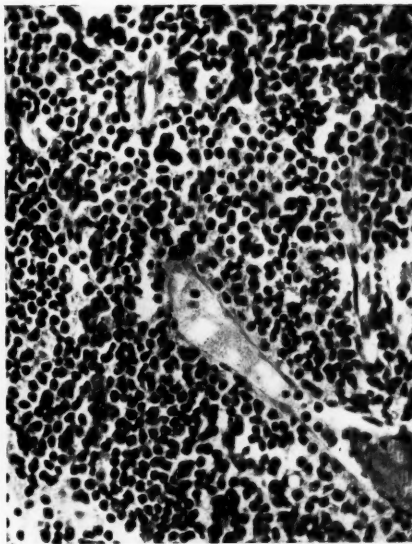


FIG. 11. Bone-marrow of Case 12.  
( $\times 380$ )



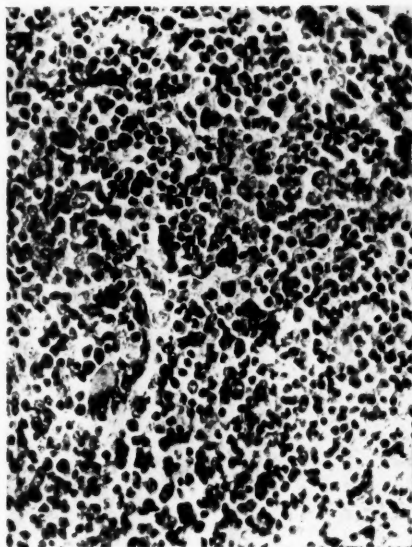


FIG. 12. Bone-marrow of Case 13.  
( $\times 380$ )

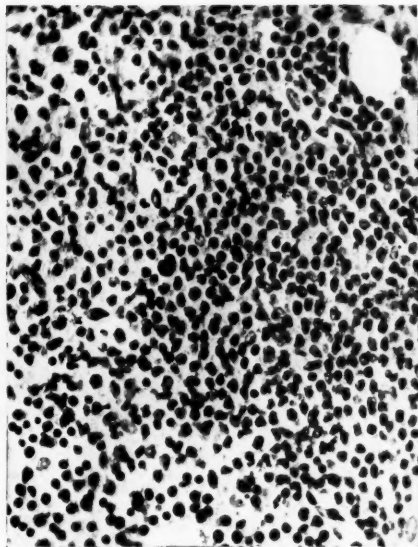


FIG. 13. Bone-marrow of Case 14.  
( $\times 380$ )

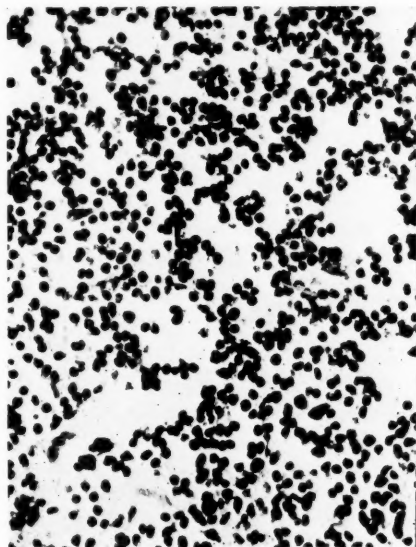
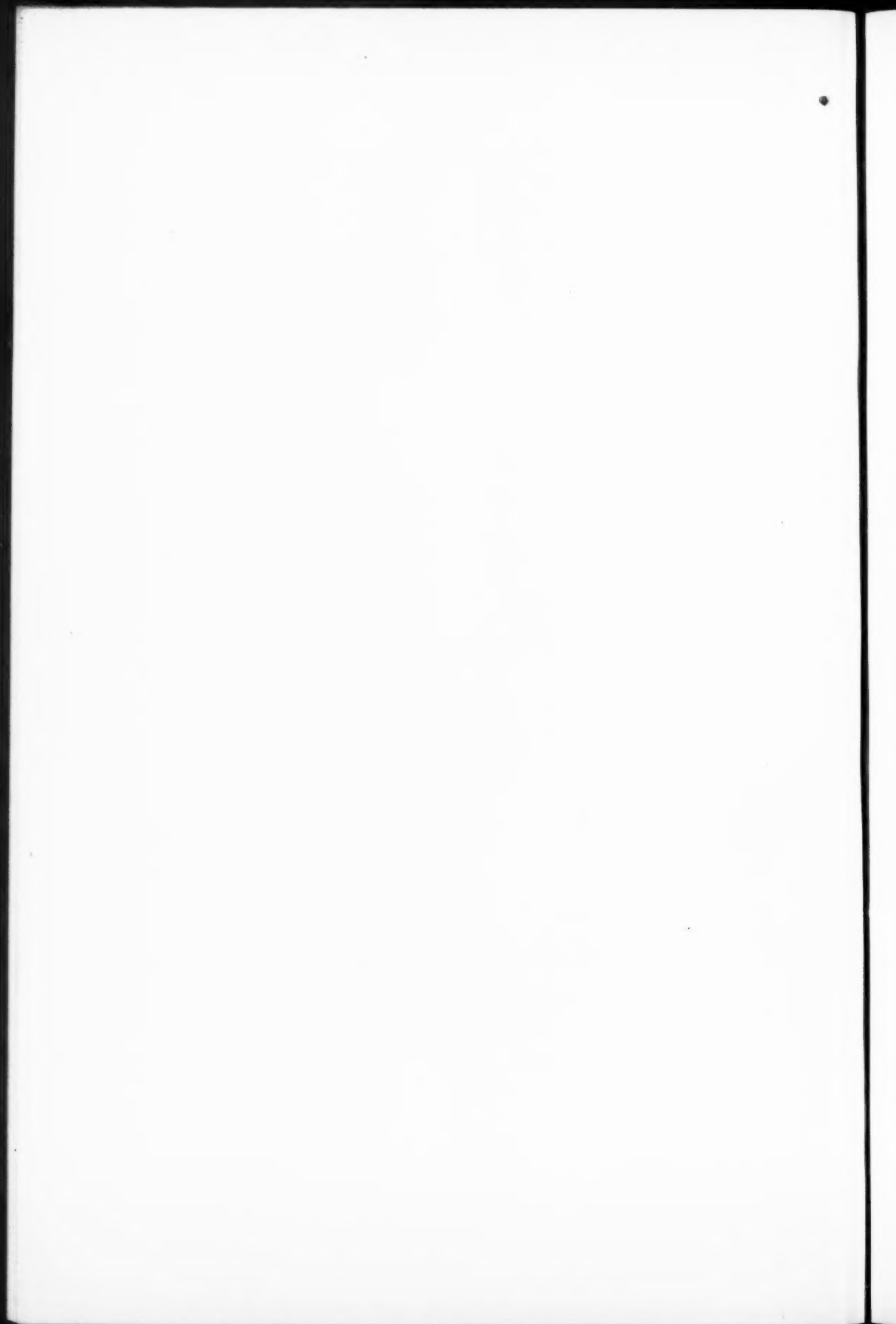


FIG. 14. Bone-marrow of Case 15.  
( $\times 380$ )



POISONING BY METHYL MERCURY COMPOUNDS<sup>1</sup>

By DONALD HUNTER, RICHARD R. BOMFORD, AND  
DOROTHY S. RUSSELL

(From the Wards of the London Hospital, and the Bernhard Baron  
Institute of Pathology)

With Plates 10 to 15

ORGANIC compounds of mercury were first used in chemical research in 1863, in therapeutics in 1887, and in the manufacture of seed dressings in 1914. Those with hydrocarbon groups of low molecular weight have been found the most toxic, and the only cases of poisoning recorded in man have been due to methyl derivatives.

Frankland and Duppa (1863) used di-methyl mercury in the course of some research work undertaken at St. Bartholomew's Hospital to determine the valency of metals and metallic compounds, and two laboratory technicians engaged in this work developed symptoms of poisoning and died (Edwards, 1865, 1866). One of them was a German aged 30 years, who had been exposed to di-methyl mercury for three months. He complained of numbness of the hands, deafness, poor vision, and sore gums. He was found to be slow and dull in manner, unsteady in gait, and unable to stand without support. There was no motor palsy, and the fundi were normal. Within a week he became rapidly worse, restless, unable to answer questions, incontinent of urine, and comatose. He died two weeks after the onset of his symptoms.

A second technician, aged 23 years, had worked in the laboratory for twelve months and had handled di-methyl mercury three months previously for a period of two weeks only. A month after this exposure he complained of sore gums, salivation, numbness of the feet, hands, and tongue, deafness, and dimness of vision. He answered questions only very slowly and with indistinct speech. There was ataxia, but no weakness of the upper limbs. Three weeks later he had difficulty in swallowing, was unable to speak, had incontinence of urine and faeces, and was often restless and violent. He remained in a confused state, and died of pneumonia twelve months after the onset of his symptoms. A third technician was affected with symptoms similar in character to those already described, but less severe in degree, and he eventually recovered. The story of these deaths has been handed down verbally from one generation of chemists to another.

In 1887 Hepp used hypodermic injections of di-ethyl mercury in the

<sup>1</sup> Received March 16, 1940.

treatment of syphilis. He gave doses ranging from 0.1 to 1.0 c.c. of a 1 per cent. solution of this substance. No patient received more than two injections, for in the meantime animal experiments had been carried out which suggested that the substance was highly toxic. The picture of di-ethyl mercury poisoning in animals was found to differ from that of poisoning by inorganic mercury compounds. There was only moderate inflammation of the intestinal tract, but the nervous system was constantly involved. An ascending paralysis was combined in some animals with ataxia. Inco-ordination of movement was noticed especially in rabbits, and motor paralysis in dogs and cats. Tremor, blindness, loss of sense of smell, transient deafness, and attacks of wrath on the slightest provocation were also noticed in many of the dogs.

*Mercury compounds used as seed dressings.* Seed-borne diseases of cereals were first treated by organic compounds of mercury by Riehm in 1914. To-day their use in the prevention of such diseases as bunt of wheat (*Tilletia tritici*) (Plate 10, Fig. 6), covered smut of barley (*Ustilago hordei*), leaf stripe of oats (*Helminthosporium avenae*), and leaf stripe of barley (*Helminthosporium gramineum*) is a well-established principle of plant hygiene (Martin, 1936). The first of these seed disinfectants to be successful was Uspulun, placed on the market in 1915 by Messrs. Bayer. It was probably of the structure  $\text{Cl}(\text{OH})\text{C}_6\text{H}_3\cdot\text{Hg}\cdot\text{OSO}_3\text{Na}$ . Germesan introduced about 1920 by the Saccharin Fabrik A.-G. contained cresyl mercury cyanide  $(\text{HO})(\text{CH}_3)\text{C}_6\text{H}_3\cdot\text{Hg}\cdot\text{CN}$ . Ceresan introduced by the I.G. Farbenindustrie A.-G. was reported to contain as the active ingredient phenyl mercury acetate,  $\text{C}_6\text{H}_5\cdot\text{Hg}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$  (Plate 11, Fig. 7). Agrosan-G, introduced by Imperial Chemical Industries, Ltd., contained mercury in the form of tolyl mercury acetate,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{Hg}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ . Of the recently introduced products one contains ethyl mercury chloride,  $\text{C}_2\text{H}_5\text{Hg}\cdot\text{Cl}$ , and another ethyl mercury phosphate,  $\text{C}_2\text{H}_5\cdot\text{Hg}\cdot\text{H}_2\text{PO}_4$ .

The relationship between the molecular structure and the fungicidal activity of organic compounds of mercury has also been investigated. Riehm (1923) determined the minimum concentration of different compounds necessary to inhibit germination of bunt spores under standard conditions. Gassner and Esdorn (1923) used a similar method and were able to demonstrate the importance of molecular structure in determining the fungicidal properties of these compounds. Thus, inhibition of germination under standard conditions was produced by different compounds in the following proportion: mercuric chloride 0.025, chlor-phenol mercury 0.07, and methyl mercury iodide 0.001. Methyl mercury iodide,  $\text{CH}_3\cdot\text{Hg}\cdot\text{I}$ , was thus the most active of the compounds tested, but was discarded by these authors on the score of its highly poisonous character. Weston and Boer (1935), employing tolyl, ethyl, phenyl, and methyl mercury compounds against a large number of seed-borne diseases of cereals, confirmed the view that the fungicidal properties decrease with increase of the molecular weight of the hydrocarbon group.



The manufacture of phenyl and tolyl mercury compounds in large quantities by Imperial Chemical Industries, Ltd. in this country and I.G. Farbenindustrie A.-G. in Germany has been carried on by automatic methods in completely enclosed apparatus. The products are used mainly in the form of dusts, though sometimes they are employed in solution. So far as is known, no mishap worse than an occasional burn on the skin has occurred in handling them. If an organic mercury compound comes in contact with the skin, warmth and redness occur after about six hours, and blistering after eighteen to twenty-four hours. The blister contains serous fluid, and the lesion remaining after it bursts may take three weeks to heal.

The purpose of this communication is to record four cases of poisoning by inhalation of methyl mercury compounds in a factory where fungicidal dusts were manufactured without the use of completely enclosed apparatus. The cases are unique because they occurred in the only factory where this substance has ever been made, and for obvious reasons it should not be made again in similar circumstances. With the exception of tremor, the symptoms of poisoning by metallic mercury, namely, salivation, stomatitis, and erethism, were absent, and the nervous system alone was involved. There was severe generalized ataxia, dysarthria, and gross constriction of the visual fields, memory and intelligence being unaffected. The illness of these men was in some ways comparable to that of the two technicians who died at St. Bartholomew's Hospital. The selective effect on certain parts of the nervous system of the chemical substances responsible was confirmed by experiments on rats and a monkey. In these animals methyl mercury compounds caused an intense and widespread degeneration of certain sensory paths of the nervous system, the peripheral nerves and posterior spinal roots being affected first, and the spinal cord and certain neurones in the middle lobe of the cerebellum later.

*Technique of manufacture of seed dressings.* In the factory where our patients worked the manufacture of methyl mercury nitrate seed dressing was carried out in two stages. The first step was the preparation of methyl iodide from methyl alcohol, phosphorus, and iodine. This was then allowed to react with mercury under the influence of the light from electric lamps, and methyl mercury iodide was formed. Flasks containing this substance as a solid were tapped on rubber sheets until the contents were loose and broken up. This work was done in a room about sixteen feet square, with four skylights, two windows, and a large double door, all of which were kept open.

In the second stage the dry methyl mercury iodide was mixed intimately with mercuric nitrate solution in a power-driven pestle-and-mortar mill. By double decomposition methyl mercury nitrate and mercuric iodide were formed. The latter, being insoluble, was separated by filtration, and an almost saturated solution of methyl mercury nitrate was obtained. The solution of this substance was diluted and mixed with an inert powder in a mechanical mixer. The mixture was damp and there was therefore no escape of dust. The damp dust was transferred to a drying chamber, and

when dry it was ground in a mill and was then ready for packing. This work was done by men wearing dust masks, goggles, and elbow gloves, working in a room about 40 feet square in which good ventilation was ensured through windows, skylights, and gaps in the walls.

*Prevention of poisoning.* Of twelve men who were exposed to methyl mercury compounds under the conditions described, but did not develop any symptoms, eight excreted mercury in the urine and four did not. The spectrophotometric test used was sensitive to 0.001 mg. of mercury per litre, so that the quantities of mercury excreted in the urine were probably very small. The fact that eight men, exposed in a similar way to the four patients, excreted mercury in the urine, yet showed no symptoms or signs of disease, suggests that most of the workers absorbed mercury compounds, but that only four of the sixteen were susceptible to them.

In the manufacture of organic mercury compounds adequate precautions must be taken to ensure that dusts and vapours do not come in contact with the skin and are not inhaled. The use of gloves and respirators is inadequate as a means of protection; the whole process of manufacture, including the final packing of the dust, should be carried out mechanically in enclosed apparatus. Compared to the factory worker the farmer runs little risk. He should, however, be protected both by warnings that mercurial dressings are poisonous, and by schemes whereby he can obtain from the seed merchant seed already dressed. The seed merchant should dress the seed in completely closed apparatus (Plate 12, Fig. 10).

#### *Case Reports*

*Case 1.* E. L., a man of 33 years (L. H. Reg. No. 30240/1937).

*Clinical history.* The patient was a labourer in a chemical factory, and he was first employed in making seed dressings five months before admission. The work involved the handling of mercury, methyl iodide, and methyl mercury iodide. A month later he developed thirst, polyuria, and intermittent glycosuria, which lasted three weeks. Investigation showed a normal response to a glucose tolerance test. After about three months of the work he complained that his whole body was going numb and tingling. He began to notice weakness of his arms and legs, and unsteadiness in his gait. His condition became worse, and after four months' employment he was put on night work at his own request, so that he no longer handled organic mercury compounds. He became clumsy, dropped trays, began to stagger about, and collapsed on the floor on several occasions. His speech became difficult and slurred, and it was noticed that he sometimes could not see objects held in front of his face.

*Previous history.* Served in the army in England and in India from 1922 to 1929. Attending a clinic with gonorrhoea.

*Family history.* Father died in diabetic coma. Mother and nine siblings alive and well.

*Condition on admission.* Thin, worried man of hysterical temperament. Afebrile. Slight exophthalmos. No abnormality in respiratory, cardiovascular, or gastro-intestinal systems. Nervous system: lies in bed, apathetic and dazed; speech indistinct and explosive in character; he hears a watch

normally, but he cannot quickly comprehend the meaning of spoken speech; cranial nerves, no abnormality detected; fundi normal; fields of vision not tested. Gross inco-ordination of upper and lower limbs. Tendon reflexes equal and exaggerated; plantar responses flexor. Clumsy movements and ataxic gait. Sensation to pin-prick and light touch unimpaired.

*Special examinations.* Blood count: red cells 4,500,000 per c.mm., haemoglobin 87 per cent. (Haldane), colour index 0.96, white cells 8,400 per c.mm., differential count normal. Blood Wassermann reaction negative.

OBJECT, 4° WHITE

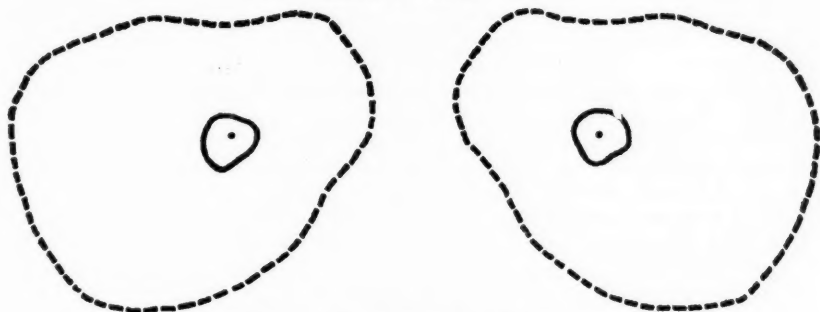


FIG. 1. The visual fields of Case 1.

Lumbar puncture: fluid clear and colourless; no excess of white cells; protein 50 mg. per 100 c.c.; Wassermann reaction negative. Urine: no albumin, no sugar, spectrophotometric test for mercury negative.

The condition was thought to be hysterical until the other cases occurred and were found to be comparable. He discharged himself after five weeks in hospital.

*Condition five months after onset of symptoms.* The patient stated that his condition was improving. His chief symptoms were a need to listen carefully to speech in order to understand its meaning, difficulty in performing co-ordinated movements with hands, unsteady gait, and difficulty in speaking. He could feed and dress himself, but only slowly and clumsily.

Physical examination (Dr. Swithin Meadows): Normally orientated in space and time; no gross memory defect; attentive and co-operative. Can understand slowly but not quickly spoken speech, whether this is loud or soft. Fundi normal. Visual acuity; right eye 6/6, left eye 6/12. Visual fields: gross peripheral constriction (Fig. 1). Loss of sense of position in nose and lips. Other cranial nerves normal. Upper limbs: no definite weakness, wasting, or alteration in tone. Considerable ataxia, especially with eyes closed. Lower limbs: power good, but impaired if he does not watch his feet. Tone normal. Moderate ataxia, worse with eyes closed. Reflexes all brisk and equal. Plantar responses flexor. Sensation: postural sense grossly impaired in all fingers and toes; stereognosis, vibration sense and two-point discrimination impaired in fingers; appreciation of pin-prick and light touch normal. Gait slow with short mincing steps; it resembles a hysterical gait, but it is definitely ataxic.

*Progress.* Three years after the onset of symptoms there was little change in the physical signs. Visual fields constricted. Fundi normal. He was able to do light unskilled work.

*Case 2.* A. H., a boy of 16 years (L. H. Reg. No. 30569/1937).

*Clinical history.* Four months before admission the patient left a technical school with distinctions to his credit. He had been described as 'a boy of more than average ability'. From this time onwards he was employed as a technical assistant in a laboratory attached to a plant for the manufacture of mercury compounds, including seed dressings. His work involved the handling of methyl iodide and of certain volatile organic mercury compounds, including methyl mercury iodide, nitrate, and phosphate, as well as of ordinary laboratory reagents. No special ventilation was provided, but he wore a mask and gloves while at work, and five weeks before admission towards the end of the third month of his work in the laboratory he first noticed 'funny numbness' starting in the tips of his fingers and toes, and spreading to his hands and feet. This feeling increased, and he began to have difficulty in performing such complicated movements as buttoning and unbuttoning his clothes. Three weeks before admission a change was noticed in his usually amiable and courteous disposition. He appeared irritable and began to use abusive language in his home. Two weeks before admission his speech became slow and difficult, and he noticed difficulty in understanding what was said to him, though his perception of sound remained unaltered. At the same time he noticed that although he could see clearly he would fail to observe certain objects in his field of vision, especially moving ones, and was therefore nearly run over by approaching motor-cars. He could see lettering clearly, but his speed of reading was much reduced. Two days later he began to be unsteady on his legs, and was seen to stagger as he walked. He was also becoming increasingly irritable and morose. Four days before admission he became obviously clumsy and had difficulty in handling a knife and fork, and in inserting food into his mouth, though his appetite remained normal. Two days before admission his determination in spite of increasing disabilities to remain at work was frustrated by his mother, who hid his trousers.

*Previous history.* Chicken-pox, measles, scarlet fever, and tonsillitis as a child; no other illnesses.

*Family history.* Father and mother and one sibling alive and well. A maternal aunt had died of amyotrophic lateral sclerosis.

*Condition on admission.* A boy of spare build but healthy appearance. Weight 9 st. 2 lb. Afebrile. No abnormality discovered in the respiratory, cardiovascular, or gastro-intestinal systems. Nervous system (Dr. Swithin Meadows): He sleeps a great part of the day, lying curled up on his right side. When roused he appears to take less than a normal amount of interest in his surroundings, but when allowance has been made for his difficulties in speech and hearing it appears that his memory and intellectual faculties are unimpaired. Orientation normal. No hallucinations or delusions. Speech dysarthric, slow, and slurred. Hearing: able to hear quite well even a low voice if spoken to slowly. He cannot understand quick speech however loud. Aural report by Mr. Charles Keogh: 'Air conduction, allowing for delay in reception, is within normal limits. Bone conduction is diminished. This phenomenon is due to slow cerebration.' Vision: can read small print. Gross peripheral constriction of visual fields (Fig. 2). Cranial nerves: fundi, pupils, and ocular movements normal; slight lower right facial weakness; loss of sense of position in tongue, nose, and lips; cranial nerves otherwise normal. Upper limbs: no definite weakness, wasting, or alteration in tone; marked inco-ordination, especially for fine movements; takes two minutes to fasten four buttons; outstretched hands wander if eyes closed, and left hand

tends to drop; finger-nose test very clumsily performed; rapidly alternating movements poorly performed. Trunk: able to sit up without using arms. Lower limbs: power fairly good; moderate pyramidal spasticity; marked inco-ordination; reflexes all present and equal; knee- and ankle-jerks exaggerated; plantar responses, right flexor, left extensor. Sensation: gross postural loss in fingers, toes, and face; two-point discrimination grossly impaired at finger-tips; astereognosis so severe in hands that he cannot tell

OBJECT, 2° WHITE

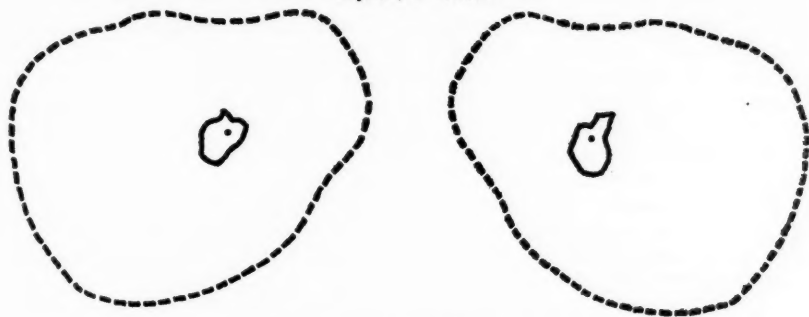


FIG. 2. The visual fields of Case 2.

with his eyes shut the difference between a coin and a bunch of keys; vibration and other forms of sensation normal. Gait very ataxic, walks on wide base, Romberg's sign positive.

*Special examinations.* Blood count: red cells 5,300,000 per c.mm., haemoglobin 95 per cent. (Haldane), colour index 0.89, white cells 5,000 per c.mm., differential count normal, reticulocytes less than 2 per cent., no abnormality seen in stained film. Blood Wassermann reaction negative. Lumbar puncture: pressure 90 mm. of C.S.F.; Queckenstedt's test normal; fluid clear and colourless; no excess of white cells; protein, 40 mg. per 100 c.c.; Wassermann reaction negative; colloidal gold curve 0012222100. Blood-urea 28 mg. per 100 c.c. Urine: no albumin or sugar, occasional leucocytes in deposit; mercury detected by spectrophotometric test.

*Progress.* After admission the patient's condition became slowly and steadily worse. He slept for increasing periods, and his speech, hearing, and general condition all deteriorated. Eight weeks after the onset of his symptoms his condition was at its worst. He lay curled up on his side, completely helpless and apathetic. His ataxia was so severe that he could not perform even the simplest movements for himself. Saliva dribbled from his mouth, and he choked and spluttered when fed. He scarcely attempted to speak, and when he did so produced explosive vowel sounds whose meaning could rarely be recognized. He could understand only the simplest statements spoken very slowly. He was severely constipated, but was never incontinent at any time. He became emaciated. Nine weeks after the onset of symptoms signs of slight improvement were noticed, and he began to take more interest in his surroundings. At the same time it became easier to feed him, and he was first made to walk up and down the ward with support on each side. He responded so much better to written than to spoken questions and requests that this method was used for communication. Thirteen weeks after the onset of symptoms he began to have massage and re-educative movements (Sir Robert Stanton Woods). By this time he could just hold a tumbler and



put it to his mouth almost unaided, though ataxia was still very obvious. His condition was thus very slowly improving. Seventeen weeks after the onset of symptoms he could still produce no articulate sounds, but he began to attempt to do so. He learned to communicate by spelling out words and sentences on a printed alphabet which he carried with him. His walking was improving, but his gait was still ataxic and 'slapping'. Two weeks later he began to perform simple movements for himself, and for the first time walked a few paces unaided. After sixteen weeks he first began to produce vowel sounds, and was treated in a speech clinic (Miss Muriel Murphy). After much patient practice in front of a mirror, the explosive consonants were gradually mastered. The lips, the tongue, and later the soft palate responded to voluntary effort, and occasionally the alveolar consonants were successfully pronounced. From then onwards his speech slowly but steadily improved. Six months after admission he could walk unaided on the level. A month later he began to use a typewriter, chiefly with his left hand, and at first slowly and laboriously. For another month he made no attempt to speak spontaneously. His general condition throughout this time continued to improve; he became better nourished, more responsive, interested in his appearance, and gradually able to do more for himself. Eight months after the onset of symptoms he walked fifty times round the hospital garden unaided, a distance of about four miles. As communication became easier it was apparent that his memory and intelligence had been little, if at all, affected, and that he had a ready sense of humour and considerable personal charm. He was keenly interested in everything around him, able to remember all that had happened, and to discuss accurately and intelligibly technical problems connected with his occupation before he was ill. From his own accounts it was apparent that even at his worst his memory and intellectual functions were little clouded, though he was quite unable to express himself. From then onwards improvement was maintained. After nine months it was possible to understand about half what he said, and he gradually gave up the use of his alphabet. Two years after the onset of symptoms he was able to walk up and down stairs quite unaided and could dress and feed himself, but in all these movements his ataxia was still very evident. A fine uniform tremor had developed in the upper limbs, head, and neck. His speech remained hesitating and explosive, but was quite readily understood. Hearing was practically normal. He could hold a pencil and a pen, write a letter in scrawling and unsteady letters, and his writing was still improving (Plate 11, Fig. 8). To those who had watched him throughout his illness it seemed likely that his actual neurological condition had improved little, if at all. His visual fields were practically unaltered since they were first charted. His ataxia was still gross, and his left plantar response was still extensor. Astereognosis was well marked, and his attempts to recognize with his eyes shut objects placed in his hand were still exceedingly poor. The optic disks remained normal. The striking improvement in the condition must be attributed to re-education, and the degree to which this was successful is a tribute to the determination of the patient and to the skill and patience of members of the nursing staff, the massage staff, and the speech clinic, who were all concerned in treating him.

*Case 3.* E. C.-L., a man of 33 years (L. H. Reg. No. 30668/1937).

*Clinical history.* Five months before admission the patient started work in a chemical factory in a department for the manufacture of seed dressings. His job was to pour a solution of 2 pounds of methyl mercury nitrate from



a jug into 28 pounds of an inert powder in a mixer. He then dried the wet mixture in trays in an oven, and finally ground the resulting product to a powder, which was packed in boxes. He repeated this process about seven times each day. The work was dusty and he therefore wore gloves and a canister respirator. After two months' work he got two burns on the right forearm. They started as blisters, the larger about an inch in diameter, and took nine days to heal. Subsequently he ceased to handle organic mercury

OBJECT,  $\frac{1}{4}$ " WHITE

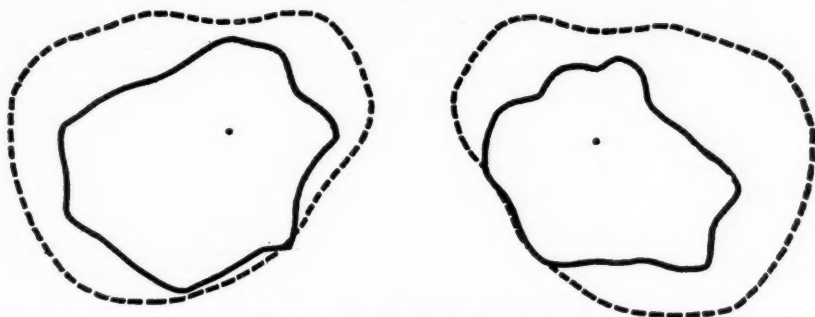


FIG. 3. The visual fields of Case 3.

compounds and worked a chlorinator in the manufacture of inorganic salts of mercury.

Three weeks before admission he noticed that he could not read as fast as usual, and a week later his fingers and then the whole of each hand tingled and became numb. One week before admission he began to have difficulty in understanding what was said to him unless it was spoken slowly and deliberately. He had trouble in fastening his collar-stud, and had to get his wife to do up the buttons of his shirt. He noticed difficulty in finding with his hand a sixpence in his pocket. His speech and hearing were normal.

*Previous history.* Tonsillitis as a child. Vision defective since schooldays. No other illnesses.

*Family history.* Mother died of cancer. Father and two siblings alive and well.

*Condition on admission.* Well-nourished, healthy-looking man. Weight 10 st. 11 lb. Afebrile. No abnormality discovered in the respiratory, cardiovascular, or gastro-intestinal systems. Nervous system (Dr. Swithin Meadows): No mental abnormality; speech rather slow; hearing normal; visual fields, slight concentric constriction (Fig. 3). Visual acuity: right eye 6/18, left eye 6/12. Fundi: disks normal, pigmented area below the right macula. Other cranial nerves normal. Upper limbs: no weakness, wasting, or alteration in tone; slight tremor and unsteadiness in finger-nose test, worse on right side; rather slow in fastening buttons; two-point discrimination impaired in finger-tips at 0.5 cm. and 1 cm.; no astereognosis. Lower limbs: no weakness or wasting; tendon reflexes normal; plantar responses flexor; two-point discrimination normal in soles; appreciation of pin-prick, cotton-wool touch, vibration, and posture all normal.

*Special examinations.* Blood count: red cells 4,300,000 per c.mm., haemoglobin 83 per cent. (Haldane), colour index 0.96, white cells 10,160 per c.mm., differential count normal. Blood Wassermann reaction

negative. Urine: no albumin, no sugar, spectrophotometric test for mercury positive.

*Progress.* Two years and six months after the onset of symptoms there was no change in the physical signs. The visual fields remained constricted and the fundi normal. He was working as an unskilled labourer.

*Case 4.* S. R., a man of 23 years (L. H. Reg. No. 30735/1937).

*Clinical history.* For two years before admission the patient had been employed in a chemical factory, at first in connexion with the manufacture of inorganic mercury compounds. Six months before admission the gums were tender and the teeth loose, but there was no salivation. Thirty-one teeth were removed in four operations. Five months before admission he was employed for four months in the manufacture of seed dressings. This work involved exposure to dusts of methyl mercury phosphate and nitrate. He wore rubber gloves, but dust got inside them and he had numerous burns on his fingers. For four weeks before admission there had been no exposure to mercury compounds. Three weeks before admission he noticed a peculiarity in vision; distant objects were blurred, and he experienced difficulty in seeing 'around corners'. There was no diplopia. At the same time there was a feeling of 'pins and needles' and numbness in the tip of the tongue and in the finger-tips, the latter sensation spreading after a few days up his arms. Slight unsteadiness of gait was noticed. One week before admission the speech became 'thicker' and slower, the movements more jerky, and the hands clumsy, causing difficulty in dressing. The vision became worse: 'I can see all right in front, but it's at the sides I can't see.'

*Previous history.* Squint and stutter since childhood. Right peritonsillar abscess one year previously.

*Family history.* Father, aged 58 years, suffers from heart disease. Mother died of strangulated hernia. Five siblings alive and well.

*Condition on admission.* Tall fair lad; edentulous. No abnormality in gastro-intestinal, respiratory, or cardiovascular systems. Nervous system (Dr. Swithin Meadows): Quiet; memory fairly good; no marked mental changes; speech normal except for stutter since childhood. Cranial nerves: pupils and fundi normal; moderate bilateral ptosis; irregular fine nystagmus on deviation to right, left, and upwards; concomitant convergent squint. Visual fields: concentric constriction which became rapidly worse as shown by perimetry tests taken four weeks (Fig. 4) and six weeks (Fig. 5) after the onset of symptoms. Visual acuity: right eye 6/6, left eye 6/12. No defect of hearing to rough tests; can understand loud, quickly spoken speech. Other cranial nerves normal. Upper limbs: no wasting, weakness, or alteration in tone; well-marked inco-ordination worse with eyes closed; difficulty with fine and rapidly alternating movements; outstretched hands tend to drop if eyes closed. Lower limbs: no wasting, weakness, or alteration in tone; well-marked inco-ordination; reflexes all present and equal; both plantar responses extensor. Postural sensibility grossly impaired in fingers, slightly impaired in toes, and absent in lips. Two-point discrimination impaired at finger-tips. Astereognosis in hands. Perception of vibration and other forms of sensation normal. Gait: well-marked ataxia, worse with eyes closed; can just walk alone with eyes open; Romberg's sign positive.

*Special examinations.* Blood count: red cells 5,200,000 per c.mm., haemoglobin 104 per cent. (Haldane), colour index 0.99, white cells 6,700 per c.mm., differential count normal, reticulocytes less than 2 per cent., no abnormality seen in stained film. Blood Wassermann reaction negative. Lumbar

puncture: no excess of white cells; protein 55 mg. per 100 c.c.; Wassermann reaction negative; colloidal gold curve 0011222110. Blood-urea varied from 34 to 64 mg. per 100 c.c. Urine: acid, cloud of albumin, slight reduction of Fehling's solution on cooling; deposit, many epithelial cells, no casts; spectrophotometric test for mercury positive.

OBJECT,  $\frac{1}{2}^{\circ}$  WHITE

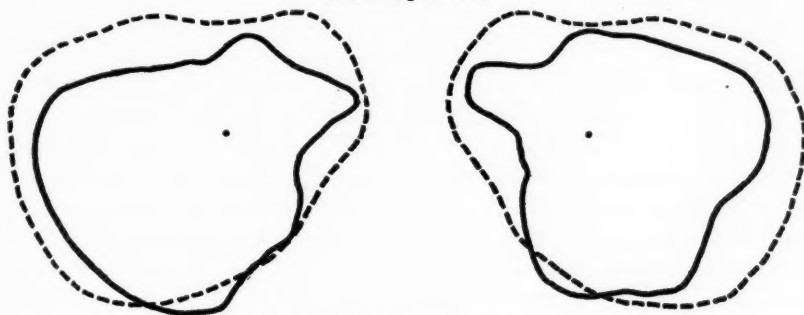


FIG. 4. The visual fields of Case 4 on April 20, 1937.

OBJECT,  $4^{\circ}$  WHITE

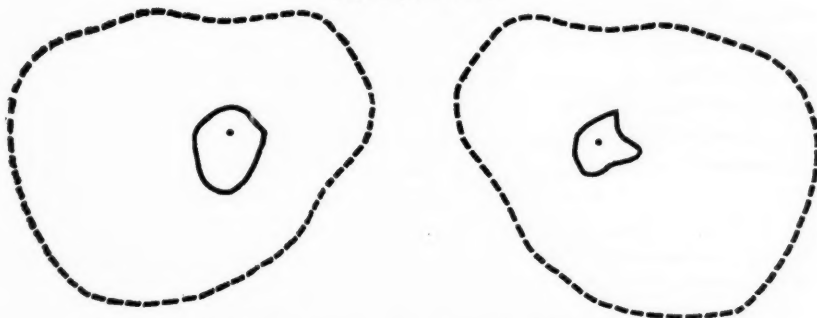


FIG. 5. The visual fields of Case 4 on May 3, 1937.

*Progress.* After admission the patient's condition became slowly and progressively worse. He became drowsy, unable to walk, unable to feed himself, and his speech became increasingly slow and hesitant. Five weeks after the onset of symptoms he was at his worst. He looked ashen and very ill, was drowsy and quite helpless, and unless disturbed remained completely apathetic. Food placed in his mouth would remain unswallowed, and his expression was that of a slobbering idiot. Speech was limited to two or three words and was almost unintelligible. From that time onwards there was a slight but very slow improvement. His general condition improved, he was less drowsy than before, and began to take a little interest in his surroundings. He began to make attempts to walk, supported by two assistants (Plate 12, Fig. 9). Eight weeks after the onset of symptoms he developed a left femoral thrombosis, which pursued an uneventful course. Six weeks later slight improvement in speech occurred; he began to make some attempts to articulate, and was able to sit up in a chair. After this little change occurred. The patient was discharged after twelve months.

His general condition was good for one who had been in bed so long. He was, however, still grossly ataxic, quite helpless, and unable to stand unaided or walk without support from two assistants. He was quite unable to feed himself or to perform the simplest act unaided. His speech was limited to a few scarcely recognizable explosive sounds. His visual fields remained severely constricted, and his plantar reflexes extensor. Three years after the onset of symptoms he was still totally disabled.

#### ANIMAL EXPERIMENTS

(R.R.B. and D.S.R.)

Four experiments were undertaken to determine firstly whether symptoms similar to those observed in the four patients could be reproduced in animals by exposure to any of the suspected poisons; and secondly to provide material for pathological study.

*Experiment I.* Fourteen healthy, adult, albino or pied Norwegian rats (nos. 1 to 14) were used. Doses of 1.0 mg. of methyl mercury iodide, methyl mercury nitrate, or mercuric iodide were administered daily to each of a group of rats, and a further group was kept under similar conditions as a control. The mercury compounds were given by stomach tube, 1 mg. of methyl mercury iodide being dissolved in 1 c.c. of olive oil, 1 mg. of methyl mercury nitrate in 1 c.c. of water, and 1 mg. of mercuric iodide in 1 c.c. of a weak aqueous solution of potassium iodide. On the nineteenth day the dose of each substance was increased to 2 mg. per diem. The rats were fed on a prepared rat food and given drinking water, both in unlimited quantities. Four rats (nos. 2, 3, 5, and 8) died shortly after the passage of the stomach tube during the first few days of the experiment. Their deaths were due to inexpert manipulation, and their tissues were used for histological comparison with those of other members of the series.

Three rats (nos. 1, 13, and 14) were given an average dose of 36 mg. of methyl mercury iodide dissolved in olive oil over an average period of twenty-nine days, and two (nos. 4 and 6) were given an average dose of 34 mg. of methyl mercury nitrate dissolved in water over a period of twenty-nine days. No abnormality was noticed for two weeks in the rats given methyl mercury nitrate and for three weeks in the rats given methyl mercury iodide. Thereafter the symptoms observed were similar in both groups; all the animals showed a rapid loss of weight. (Methyl mercury nitrate rats: average weight before experiment 280 gm., at conclusion of experiment 175 gm. Methyl mercury iodide rats: before experiment 366 gm., after 270 gm.)

In the fourth week all five rats became obviously ill; in each case the first abnormality noted was a clumsiness in the use of the hind legs, which appeared to be due partly to weakness and partly to ataxia. At the same time the animals' feet became redder and colder than those of the controls. As the condition progressed the hind legs were severely affected, so that the animals' hind quarters swayed from side to side when they moved. They

sat huddled up, with little interest in food or drink unless disturbed. When disturbed those worst affected moved with their front legs and dragged their hind ones. In some animals it was thought that the front legs were also slightly affected. All the rats became moribund within a week of showing symptoms, except rat no. 14 (methyl mercury iodide) which survived for eleven days.

The rats treated with mercuric iodide and the rats kept as normal controls all maintained their weight and showed no abnormality.

For the remaining experiments a wooden box fitted with a glass window was provided and was made as nearly as possible air-tight. An inlet and an outlet pipe were inserted. The outlet was connected to an electrically driven pump. The inlet was connected to a small glass chamber, in which there was placed about 10 gm. of crystalline methyl mercury iodide, so that air, laden with the vapour of methyl mercury iodide, could be drawn through the box. The exhaust from the pump was bubbled through two bottles of strong caustic soda, after which the smell of a methyl mercury compound could not be recognized.

*Experiment II.* In this experiment a cage of four rats (nos. 15 to 18) was placed in the box for periods of about eight hours a day, an average exposure of 156 hours being given in twenty-two days. The rats in this experiment were not weighed. From the beginning it was noticed that the rats usually kept to the end of the cage away from the inlet tube. They either slept or spent much of their time rubbing their noses and faces. Their eyes were reddened, and some had a crusted serous discharge about their nostrils. At times they appeared dazed; after the tenth day some of them had attacks of hiccup. On the fifteenth day of exposure they appeared irritable; when disturbed they would bite each other's tails and ears, and for the first time two of them bit the hand that fed them. On the nineteenth day one rat (no. 15) had become severely ataxic, so that it fell over when it shook itself. Within a few days the other three (nos. 16, 17, and 18) were similarly affected, and died or rapidly became moribund.

*Experiment III.* In this experiment ten rats (nos. 19 to 28) of average weight 270 gm. were exposed under similar conditions for shorter periods. Two rats (nos. 19 and 20) were removed on the eighth day, after thirty-seven hours' exposure, and remained apparently unaffected except for some loss of weight which was afterwards rapidly regained. On the fourteenth day, after sixty-four hours' exposure, rat no. 28 appeared slightly clumsy in the hind legs and was therefore not exposed again. The seven remaining rats were exposed for the last time on the sixteenth day (total exposure seventy-one hours). By the twenty-first day the average weight had fallen to 226 gm., and two of the rats (nos. 25 and 28) were unmistakably clumsy with their hind legs. One other rat (no. 22) became clumsy on the twenty-fifth day, nine days after the last exposure.

Of the original ten rats, therefore, three (Group A) were definitely affected, became grossly ataxic, particularly in the hind legs, and were at times



incontinent; of these three, one (no. 25) developed symptoms five days after the last exposure, showed symptoms for eleven days, and died on the thirty-second day; one (no. 28) developed symptoms on the fourteenth day, with no latent period after exposure, and was killed when found moribund on the thirty-sixth day; and one (no. 22) developed symptoms nine days after the last exposure, and was killed at the end of twelve weeks. By this time the general condition of this animal had improved and it was increasing in weight. Its gait, however, was jerky, and the hind legs were often dragged in walking. At times, notably about three weeks before death, it was unable to climb up on to its cage. Examination of the blood by Dr. A. M. Barrett a few days before death showed a normal picture according to the findings of Wintrobe, Shumacker, and Schmidt (1936). Four more rats (Group B) were thought to be slightly clumsy with their hind legs, but the condition did not progress after exposure ceased; these were killed six months later. The remaining three rats (Group C), apart from temporary loss of weight, appeared quite unaffected.

*Experiment IV.* A fully grown female monkey (*Macacus rhesus*), weighing 4 lb. 12 oz. at the end of the experiment, was exposed to methyl mercury iodide vapour in the same box used in the experiments on rats, and under similar conditions. On the first day the animal was placed in the box for one and a half hours without exposure to methyl mercury iodide vapour. She remained active and appeared in no way distressed. Thereafter she was exposed to the vapour for daily periods increasing from one to seven and a half hours until a total of seventy-one hours' exposure had been given in twenty-one days. During this time she became obviously thinner; towards the end of it she began to appear subdued and somewhat bedraggled. After sixty hours' exposure she sat in a more flexed position with fore as well as hind feet on the floor of the cage. At times she coughed, sneezed, and brought up small quantities of mucus, and her conjunctivae were reddened.

On the twenty-fourth day, three days after the last exposure, she was very quiet and sat holding the bars of the cage. When she was disturbed she appeared irritable, weak in the hind legs, and clumsy in her movements. Though usually extremely agile, she almost fell over when crossing her cage and had to clutch at its bars to save herself; she also knocked over her milk bowl.

On the twenty-fifth day her condition was worse, and the fore limbs were affected. She snatched her food clumsily, dropped it, and had difficulty in picking it out from the hay; she then sometimes attempted to pick it up with her mouth. Her eating had become untidy, and she ceased to stuff food into her cheeks, as was her usual custom.

On the twenty-sixth day, five days after the last exposure, she was miserable, weak, and severely ataxic. She was found prostrate on the bottom of her cage. On attempting to get up she fell over backwards. Efforts to feed her with milk from a pipette were unsuccessful, and she was therefore killed with chloroform.



*Pathological Examination*

*Experiments I and II.* The four rats (nos. 2, 3, 5, and 8) that were lost during the first few days of Experiment I from faulty manipulation of the stomach tube showed no histological abnormality of the nervous system. They will not be discussed further. The pathological changes observed in the remaining animals in Experiment I were indistinguishable from those found in Experiment II. They will therefore be described together.

*Macroscopic examination.* A variable degree of emaciation was present in seven of the nine rats. In five of these pinhead and linear haemorrhagic erosions were found in the squamous and glandular portions of the stomach. Severe cloudy swelling of the kidneys was observed in three. Chronic abscesses of the lung, of the kind prevalent in laboratory rats, were found in five animals. The other tissues appeared healthy.

When the examination of the internal organs was complete the brain and upper part of the spinal cord were exposed by removing the bone, and the muscle was cleared from the remainder of the vertebrae. The central nervous system was then fixed *in situ* in 4 per cent. saline formaldehyde. By this means the danger of trauma and consequent production of artifacts in the myelin sheaths of the nerve roots and spinal cord was minimized. The dissection was completed when the tissues had become hardened.

*Microscopic examination.* Coronal sections of the brain, transverse sections of the spinal cord, and longitudinal sections of the optic and trigeminal nerves, a selection of the spinal nerve roots and peripheral nerves were examined both by the frozen-section technique and by different stains after embedding in paraffin. While the Marchi preparations of the spinal cord were embedded in celloidin in the usual way, corresponding preparations of nerve roots and peripheral nerves were teased in pure glycerine under a binocular dissecting microscope as recommended by Duncan (1930). This method was preferred on account of the minute size of some of the structures, for example the spinal nerve roots, and proved both satisfactory and simple.

*The nervous system.* In all animals there was a severe degeneration of Wallerian type in the peripheral nerves, the posterior spinal roots, and the trigeminal nerves. The peripheral nerves examined were the sciatic, femoral, and portions of the brachial plexus dissected from beneath the scapulae. In the earliest stage there was little Sudanophil material in the sheaths, but, as shown by Spielmeyer's method in frozen sections, there was great fragmentation of the myelin into ovoid masses and globules of varying size (Plate 12, Fig. 11). Teased Marchi preparations showed a corresponding early degeneration of the myelin sheaths. In a rat (no. 15, Expt. II) which had exhibited symptoms for two days before death there were abundant Sudanophil droplets in the sheaths. A comparison of the changes in the different specimens examined showed that the nerves of the hind limbs, the corresponding posterior spinal roots, and the trigeminal nerves were affected with somewhat greater severity than the nerves of the brachial plexus. At no stage

did the anterior spinal roots show any change beyond the rare finding of one or two degenerating fibres in a single preparation. The cell bodies of neurones in the posterior root and Gasserian ganglia occasionally showed slight eccentricity of the nucleus accompanied by chromatolysis. Pyknosis was rare. No definite changes were present in the brain and spinal cord, with the exception of rat no. 14 (Expt. I) where a positive Marchi reaction was obtained in the posterior columns of the cord. This rat developed symptoms eleven days before death, thus surviving for a longer period than the others of this group (see Expt. III). The cerebellum of this rat also showed an early stage of a degeneration which will be described under Expt. III.

In one rat only (no. 16, Expt. II) the optic nerve showed a diffuse degeneration of the myelin sheaths, and small collections of fat-granule cells amongst the fibres. There was no inflammatory exudate apart from these phagocytes. The optic nerves were normal in six other rats of this series; they were not examined in two.

*Other organs.* In all the animals in Expt. II the conjunctiva showed acute purulent inflammation and, in a lesser degree, there was an acute interstitial keratitis. In the kidneys great oedema was associated with severe dropsical and hyaline-droplet degeneration of the epithelium of the convoluted tubules. In places there was tubular necrosis, and the lumina were often blocked with cellular debris. There was a little fatty degeneration in a few groups of convoluted tubules. The presence of a good many karyokinesis in the lining cells afforded evidence of epithelial regeneration. The spleen showed a conspicuous storage of iron pigment in the macrophages of the pulp, and a variable degree of acute inflammation.

*Experiment III.* In this experiment, in which the rats received a smaller dose by inhalation and survived for longer periods, the following additional features were observed:

(I) *Group A (exhibiting symptoms).* *Nervous system.* A positive Marchi reaction was obtained (Plate 13, Fig. 12) in the posterior column in all three rats, being conspicuous in rats nos. 25 and 28, which died eleven and twenty-two days respectively after the onset of symptoms, and slight in rat no. 22 which was killed after twelve weeks. It will be recalled that rat no. 14 of Expt. II showed a similar degeneration of the spinal cord. As shown in Plate 13, Fig. 12, the degeneration involved the dorsal two-thirds only of the posterior columns, the anterior third being occupied in the rat by the crossed pyramidal tracts. A more advanced stage of degeneration, demonstrable by the Weigert-Pal method, was present in rat no. 22 (Plate 13, Fig. 13), but in none of the rats that died at earlier stages. Plate 13, Fig. 13, also shows the severe wasting of the posterior roots.

In the brain-stem a degeneration of the descending or spinal root of the trigeminal nerve was present (Plate 14, Fig. 16). No evidence of degeneration was found in the ascending or mesencephalic root of the trigeminal nerve. In these rats and in rat no. 14 of Expt. I there was also a patchy degeneration in the granular layer of the middle lobe of the cerebellum. At

the earliest stage recognized (eleven days after the onset of symptoms) there was severe pyknosis and karyorrhexis of the cells in the affected areas. At twenty-three days (rat no. 28) there were, in addition, many small concentrically laminated haematoxyphil bodies amongst the degenerating cells (Plate 13, Fig. 14). These appeared to arise as minute spheres in the cytoplasm of degenerating cells, the larger forms being extracellular. In the early stages they gave negative reactions for iron, calcium, and amyloid material, and appeared to be of an albuminous nature. In a rat (no. 22) killed twelve weeks after the onset of symptoms the bodies were much larger and then gave a positive reaction with von Kossa's method for calcium (Plate 13, Fig. 15). They gave no reaction for iron. Their presence was not associated with any demonstrable change either in the neighbouring Purkinje cells or in the myelinated fibres of the adjacent white matter. An idea of the size and distribution of the foci is seen in Plate 14, Fig. 16.

No changes were found in the cerebral hemispheres or optic nerves in these rats.

*Other organs.* A later stage of nephritis was demonstrated in rats nos. 14 and 28 by the presence of rays of early fibrosis in the cortex in which were present numerous fibroblasts, plasma cells, and a few neutrophil leucocytes. The glomeruli and blood-vessels were unaltered. In rat no. 25 albuminous and slight fatty degeneration of the tubules only was present. In rat no. 22 the kidneys were normal.

(II) *Group B.* The four rats of this group, thought to be slightly affected at the end of the experiment, were killed after twelve weeks had elapsed. Two of them showed a very slight degeneration of the posterior columns in frozen sections stained with Sudan III and in paraffin sections stained with Loyez' haematoxylin. Other parts of the central nervous system appeared normal. The two remaining rats were unaffected.

*Experiment IV (Monkey). Macroscopic examination.* Apart from slight congestion and cloudy swelling of the kidneys, the organs appeared healthy to the naked eye. The brain and spinal cord were removed and fixed in 4 per cent. saline formaldehyde. Segments of the right vagus, left sciatic, right anterior tibial, right ulnar, right median, and right radial nerves were pinned, without stretching, on a cork float during fixation.

*Microscopic examination.* Marchi preparations of the peripheral nerves were made, as in the rats, by teasing in glycerine. All showed early focal degeneration of the myelin sheaths (Plate 14, Fig. 17). Black droplets the size of, or slightly larger than, red blood corpuscles appeared most frequently in the sheaths near the nodes of Ranvier. Ovoid or sausage-shaped masses were rarer. The order of severity of the degeneration was approximately (1) median, ulnar, and radial, (2) vagus and sciatic, (3) anterior tibial. Frozen sections stained with Sudan III showed no fatty droplets in the sciatic nerve and posterior spinal roots. In the posterior root ganglia and the Gasserian ganglion severe degeneration of the ganglion cells was accompanied

by considerable leucocytic infiltration both of the interstitial tissue and of cells in which karyorrhexis was taking place (Plate 14, Fig. 18). The capsular cells in these also showed proliferation and occasionally contained a little fat. The myelin sheaths in the trigeminal nerve were often broken up into droplets and sausage-shaped masses of variable size. In Spielmeyer preparations of a lumbar posterior root ganglion there was considerable fragmentation of the myelin sheaths within the ganglion, but little in the central and distal segments of the posterior root, and none in the attached anterior root.

No histological changes were present in the spinal cord. Sections through different parts of the cortex, basal ganglia, and brain-stem showed occasional foci in which the sheaths of perforating vessels were infiltrated with a few leucocytes, small lymphocytes, and monocytes (Plate 15, Fig. 19). There was no meningitis. In addition the grey matter of the cerebrum and brain-stem was very sparsely infiltrated with neutrophil leucocytes which tended to lie against the cell bodies of the neurones. Preparations to demonstrate microglia and oligodendroglia showed remarkable microglial activity both in the cerebral cortex and in the basal ganglia. The cells were for the most part greatly swollen and of bizarre form (Plate 15, Fig. 20). Many of them formed greatly elongated rod cells such as characterize general paralysis of the insane; such cells often lay in close apposition to the apical dendrite of the pyramidal cells. In other places they were wrapped about the bodies of degenerating neurones. The oligodendroglial cells with their processes appeared normal. Bielschowsky preparations showed many normal nerve-cells, interspersed amongst which were a considerable number which showed all stages of disintegration. Both the frontal and occipital cortex were affected with apparently equal severity. The cerebellar cortex was unaffected, but the nuclei in the roof of the fourth ventricle were very sparsely infiltrated with leucocytes.

Sections through the optic nerve and eyeball showed no histological changes in the nerve or retina. There was, however, severe degeneration of the myelin sheaths of the ciliary nerves in the sclerotic coat. There was leucocytic infiltration of the conjunctiva, the cornea being unaffected.

*Other organs.* Lungs: the walls of the bronchi and adjacent tissues were infiltrated with neutrophil leucocytes, but there was no definite consolidation. Both liver and myocardium showed focal fatty degeneration. In the kidneys the tubules had undergone albuminous, with a little fatty and hyaline-droplet, degeneration. There was much desquamation of cells, mixed with cellular and eosinophil debris, into the lumina. The glomeruli were normal save for albuminous degeneration of the epithelium of Bowman's capsule. A few leucocytes were sparsely scattered throughout the interstitial tissue of the cortex. There was acute inflammation of the pulp of the spleen. The mucosa of the stomach showed a focus of subacute inflammatory reaction without ulceration.

*Discussion*

The above experiments show that a sensory nervous disturbance of wide distribution was constantly induced by the exposure of animals to methyl mercury iodide and methyl mercury nitrate. The effects were the same whether the substance was given by ingestion or by inhalation; symptoms were not observed until the animals had been exposed for a period of from two to three weeks. In rats nos. 22 and 25 (Expt. III) a short latent period was observed between the termination of exposure and the development of neurological symptoms; a similar latent period occurred in the monkey before the onset of severe neurological symptoms. The symptoms, as in the human cases, appeared principally to consist of severe ataxia with loss of sense of position and of muscular co-ordination. The affection was far more severe and generalized in the monkey than in the rats, which is remarkable in view of the fact that the monkey received a much smaller dose in proportion to its size than the rats in Expt. III, only a few of which were affected. This suggests that the primates may be more susceptible than rats to the organic compounds of mercury.

The histological lesions produced were uniform throughout the rat experiments, consisting, in the early stages, of a severe Wallerian degeneration in the peripheral nerves, posterior spinal roots, and trigeminal nerve, followed later by degenerations in the posterior columns and the descending root of the trigeminal nerve. It is of interest that the mesencephalic root of the trigeminal was unaffected since this has been considered to carry the proprioceptive fibres to the muscles of mastication. An appreciable lag was observed before degeneration could be demonstrated in the spinal cord, the earliest examples being in two rats in which death had taken place eleven days after the onset of symptoms. This difference in reaction of the extramedullary and intramedullary segments of the nerves has been recognized by Richter (1935) who records that eighteen days after cross-section of a spinal root, he found lipoid stages of degeneration in the extramedullary segment, whereas only a Marchi-stage of the degeneration had been reached in the intramedullary course of the affected fibres.

The focal degeneration of the cells of the granular layer of the middle lobe of the cerebellum observed in the later stages of intoxication in the rats was the only parenchymatous change found in the brain in these animals. It was not correlated with any alteration in the spino-cerebellar tracts or in the neighbouring Purkinje cells. Since it is not a form of neurone degeneration recognized in human pathology, its significance is difficult to estimate.

In the monkey, on the other hand, the cerebellar cortex was unaffected, but the grey matter of other parts of the brain, notably the cerebrum, showed a diffuse encephalitis associated with the disintegration of many neurones and a degree of microglial activity comparable with that seen in severe general paresis in human subjects. It is remarkable that the oligodendroglial cells



in such areas were devoid of 'acute swelling', a change that is known to accompany severe intoxication (Penfield and Cone, 1926).

The degeneration of the optic nerve found in one rat is of doubtful significance in relation to the mercurial poisoning, in view of the normal appearance of this nerve in the other rats and in the monkey. It is not known whether peripheral vision was affected in these animals.

Of the other tissues examined the conjunctiva and cornea demonstrated the irritating effects of volatile methyl mercury iodide, since the inflammation was confined to those animals that had received the poison by inhalation. It has long been recognized that inorganic mercury compounds cause a profound degeneration of the kidneys, and the organic compounds clearly share in this property. Acute stages of degeneration and, in a few rats, the early stages of fibrosis were observed in these experiments. Acute inflammation of the spleen and, in the rats, much siderosis were also constantly present. The significance of this is obscure. In one rat, exhibiting a chronic stage of the intoxication, an examination of the blood shortly before it was killed revealed no abnormality.

The clinical course taken by these experimental animals offers so close a parallel to that shown by the human subjects that the pathological basis of the condition is probably common to both. The human symptomatology suggests that a widespread peripheral neuritis was followed by a degeneration of the posterior columns. The tabetic picture is complicated by a corresponding sensory disturbance of the trigeminal nerve and a marked constriction of the visual fields. While the trigeminal changes were demonstrated experimentally to be due to an intense Wallerian degeneration of the fifth nerves, the visual disturbance remains unexplained. The retina and optic tracts appeared normal in the monkey and in all but one rat. In the monkey, however, the cerebral cortex showed an encephalitis resembling that of general paralysis of the insane. The absence of similar changes in the rats indicates a difference in the susceptibility of the cortical neurones in different species. Hence it may well be that in man the optic tracts are involved in a manner that awaits demonstration. The presence of degeneration in the granular layer of the middle lobe of the cerebellum in some rats suggests that the ataxia observed in the human subjects may have been in part of cerebellar though predominantly of posterior column origin.

#### *Summary*

1. Seed disinfectants containing organic mercury compounds are used to prevent smut diseases of cereals. Some of these compounds are toxic to man and animals, and it has been found that those with hydrocarbon groups of low molecular weight are the more actively fungicidal and toxic.
2. Four cases of poisoning resulting from the inhalation of methyl mercury compounds are recorded. With the exception of tremor, the symptoms of poisoning by inorganic mercury were absent, and the nervous system



alone was affected. Severe generalized ataxia, dysarthria, and gross constriction of the visual fields were present in all the cases, and one or both plantar responses were extensor in type in two. Memory and intelligence were unaffected.

3. Experiments on a number of rats and a monkey showed that methyl mercury iodide and nitrate damage selectively certain parts of the nervous system. In the rats, on which multiple observations were possible, the peripheral nerves and posterior spinal roots were affected first, and the posterior columns and the granular layer of the middle lobe of the cerebellum later.

4. The correlation of the clinical picture observed in human cases with the pathological findings in experimental animals is discussed.

5. Measures necessary to prevent poisoning by organic mercury compounds in the manufacture and use of seed dressings are outlined.

It is a pleasure to acknowledge the kindness of the employers of our patients. They supplied us with detailed information and gave us free access to their works. We are grateful to Drs. George Riddoch, Russell Brain, Swithin Meadows, and Henry Wilson for their help and advice in handling the cases, and to Dr. Richard Asher for assistance with the animal experiments. For their help with chemical problems we are indebted to Messrs. J. R. Boer, G. Six, and R. T. Bowler. We gratefully acknowledge the kindness of Professor Harris in giving us accommodation for animal experiments in the Department of Physiology of the London Hospital Medical College.

For permission to use Figs. 6 and 7 we are indebted to Bayer Products, Ltd., and for Fig. 10 to E. R. and F. Turner, Ltd., Ipswich. We wish, however, to make it clear that neither of these firms was in any way concerned with the production or handling of the substances responsible for the poisoning described in this paper.

Dr. Dorothy S. Russell carried out the histological investigations whilst working for the Medical Research Council.

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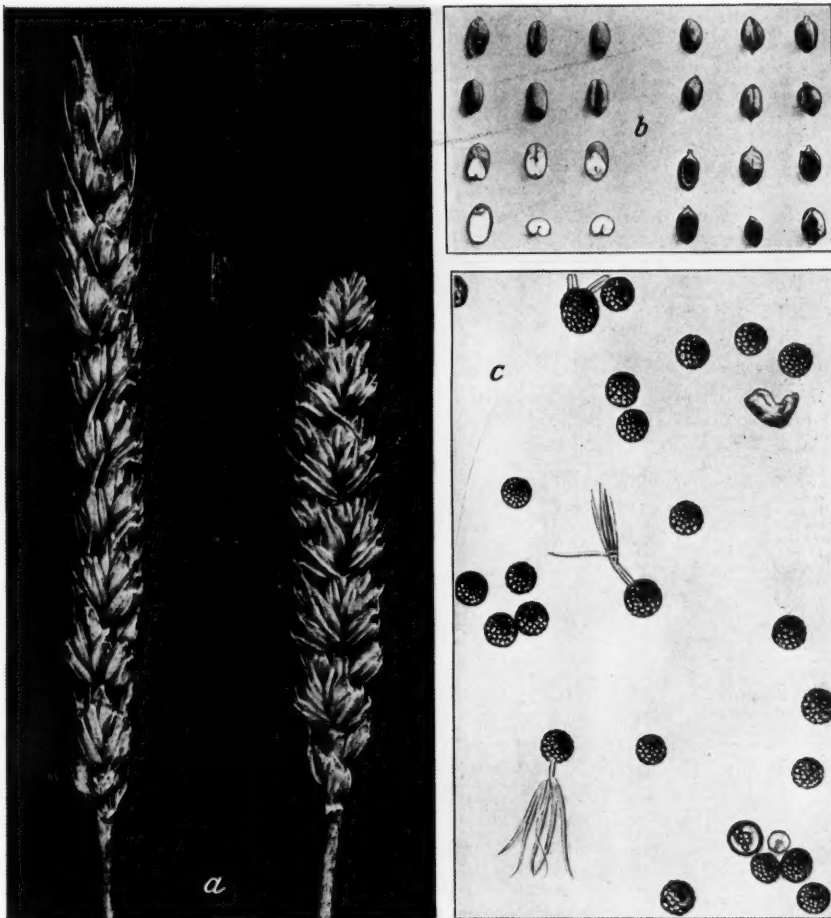


FIG. 6. Bunt of wheat (*Tilletia tritici*)

- a.* Healthy wheat ear on the left, bunted ear on the right. The chaffy scales are pushed apart, but otherwise the external appearance is little altered.
- b.* Clean grain on the left, bunted grain on the right. Each bunt ball is a black mass of 4 to 9 million spores.
- c.* Photomicrograph of germinating spores, each about 0.02 mm. in diameter.





FIG. 7. Effect of phenyl mercury acetate on oats affected by leaf stripe (*Helminthosporium avenae*). The treated seedlings are on the left, the untreated on the right.

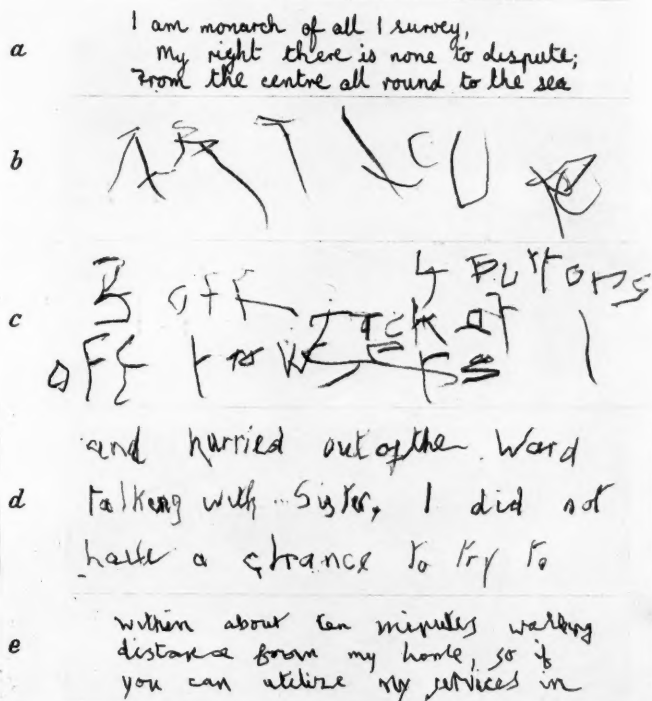


FIG. 8. Handwriting in Case 2. a. Before illness began. b. Nine months after onset of first symptoms. c. Twelve months after. d. Eighteen months after. e. Two years after





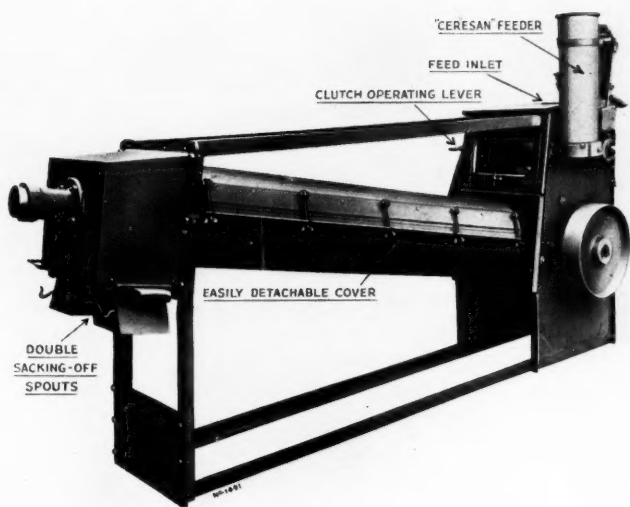


FIG. 10. The Turner Ceresan Seed Dresser



FIG. 9. Case 4



FIG. 11. Rat no. 17. Longitudinal section of posterior lumbar root showing fragmentation of myelin sheaths. Spielmeyer.  $\times 470$



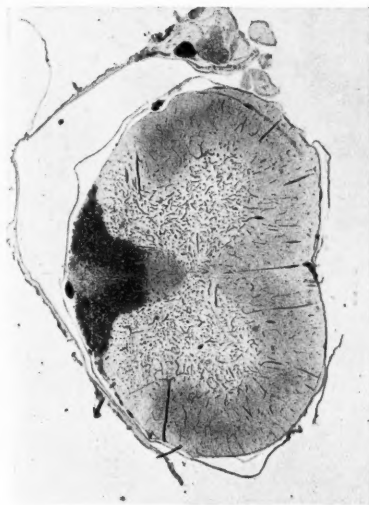


FIG. 12. Rat no. 25. Cervical cord showing early degeneration of posterior columns. Marchi.  $\times 19$



FIG. 13. Rat no. 22. Cervical cord showing later stage of degeneration of posterior columns. Note wasting of posterior root. Weigert-Pal.  $\times 12.5$

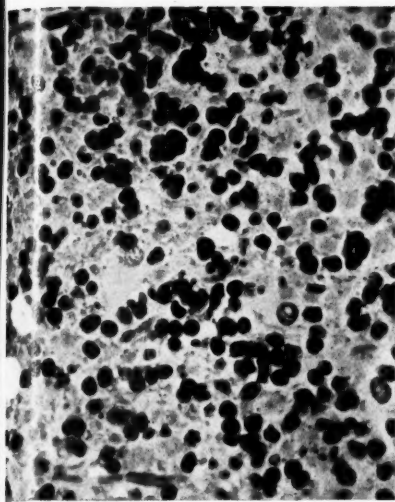


FIG. 14. Rat no. 28. Granular layer of cerebellum showing pyknosis of nuclei amongst which are numerous, more lightly stained, spherical bodies. Haematoxylin and eosin.  $\times 500$

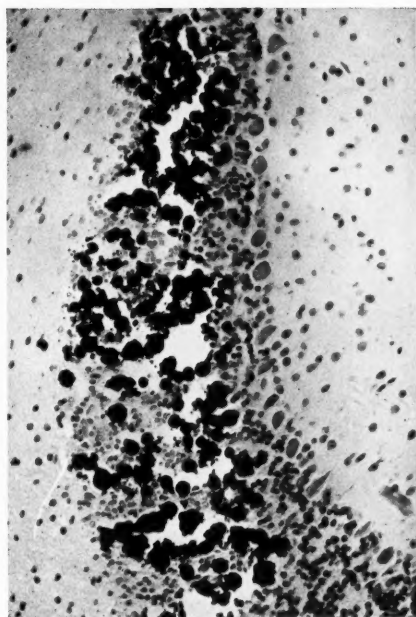


FIG. 15. Rat no. 22. Cerebellar cortex showing later stage of degeneration of granular layer now containing numerous calcospherites (black). Von Kossa.  $\times 160$



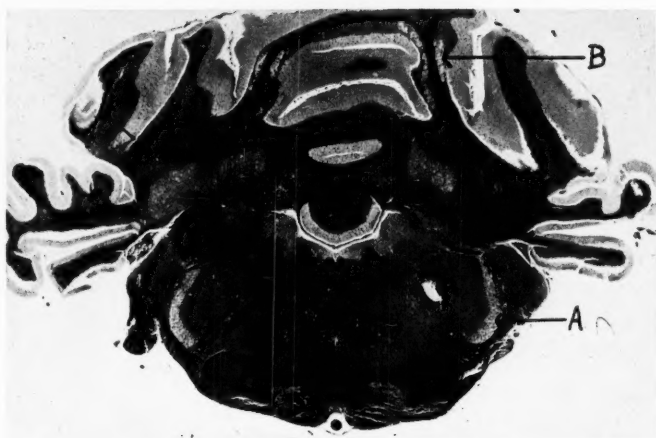


FIG. 16. Rat no. 22. Cerebellum and medulla oblongata showing (A) pallor of descending root of trigeminal nerve, (B) pale areas in granular layer of middle lobe of cerebellum, corresponding to foci shown in Fig. 15. Loyez' haematoxylin.  $\times 8.6$

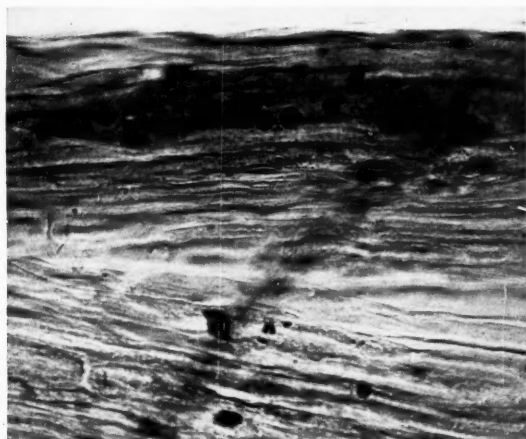


FIG. 17. Monkey. Ulnar nerve showing early degeneration of myelin sheaths. Marchi.  $\times 370$

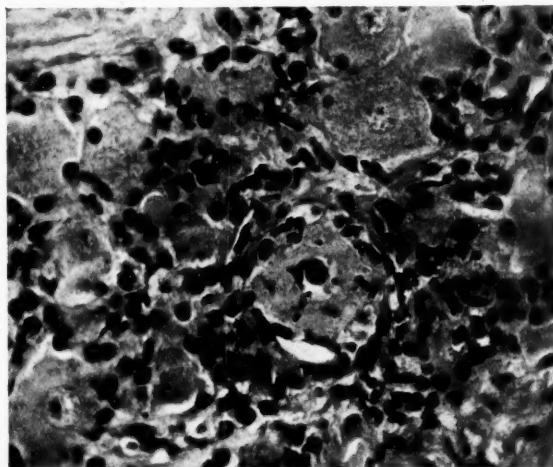


FIG. 18. Monkey. Posterior root ganglion showing degeneration of neurone in centre of field. Haematoxylin and eosin.  $\times 370$





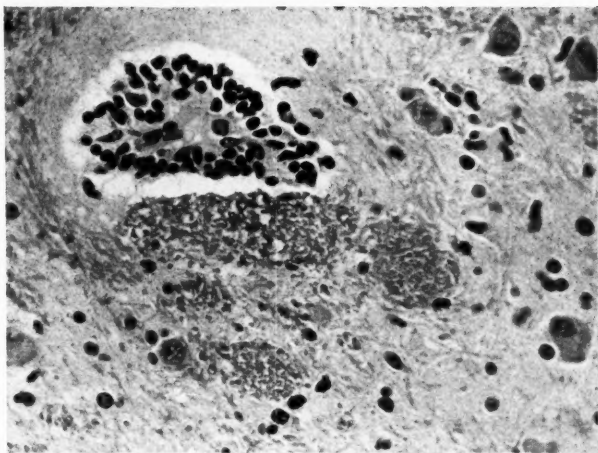


FIG. 19. Monkey. Optic thalamus showing perivascular cuffing. A few neutrophil leucocytes are present in the adjacent nervous tissue. Haematoxylin and eosin.  $\times 370$

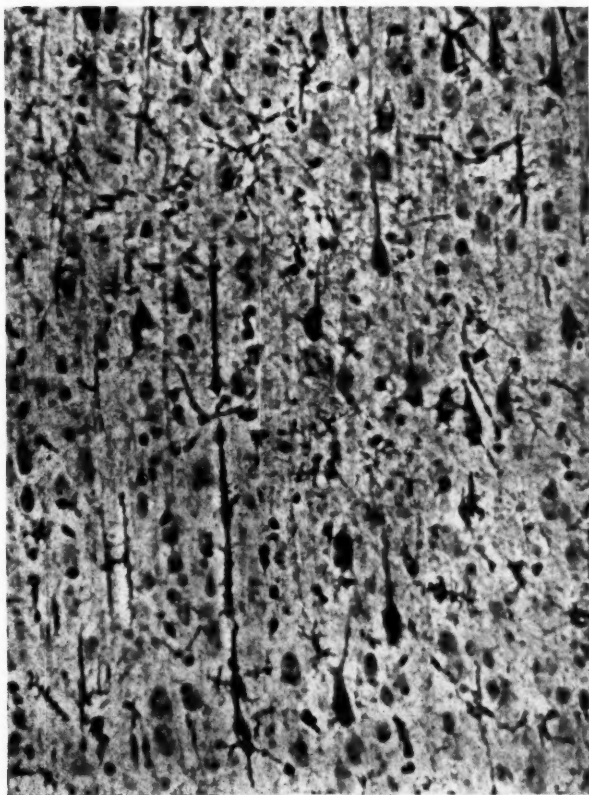
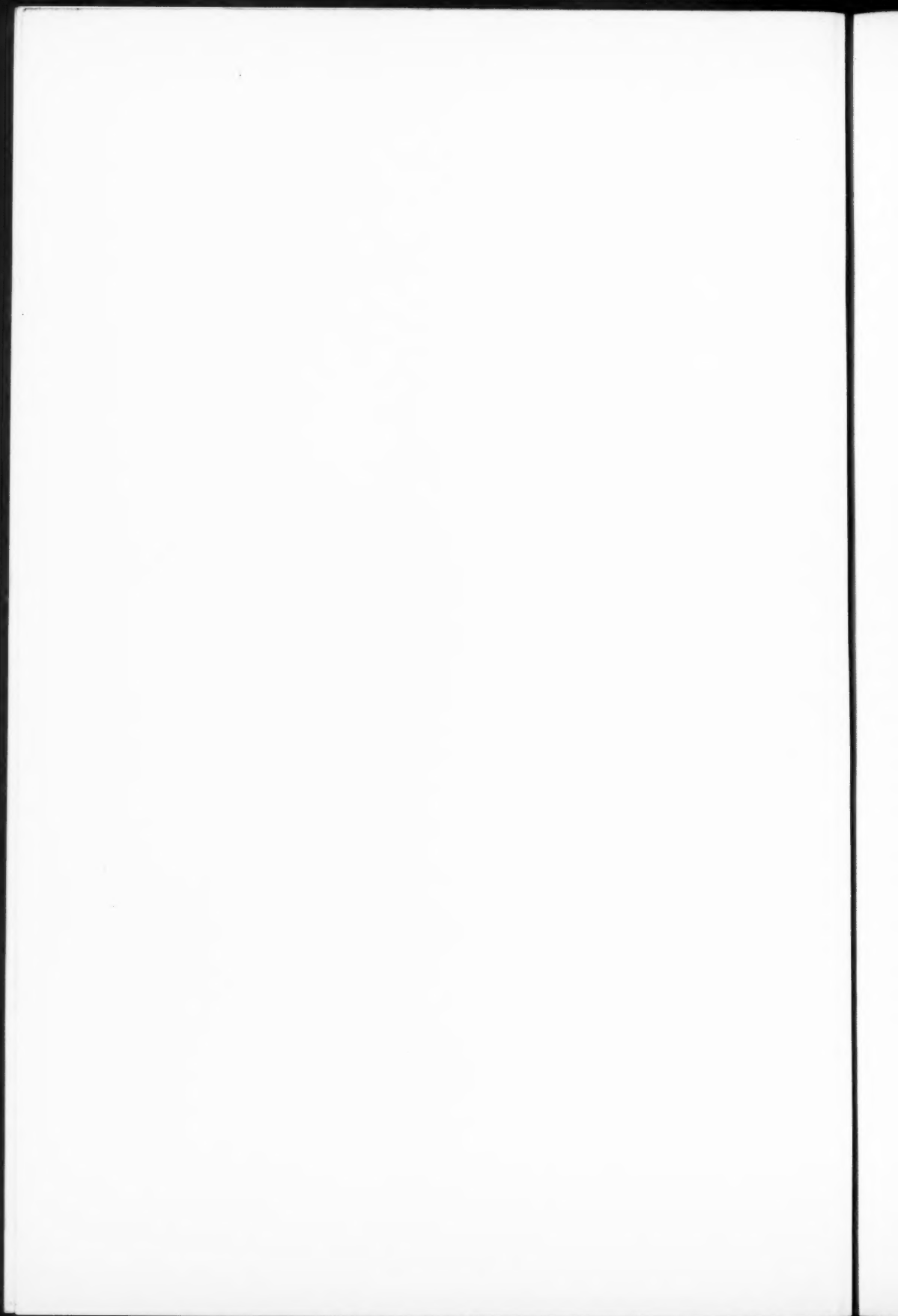


FIG. 20. Monkey. Frontal cortex showing increase of microglia with formation of conspicuous rod cells (left of centre). Penfield's modification.  $\times 220$



LIVER FUNCTION IN THYROTOXICOSIS<sup>1</sup>

By N. F. MACLAGAN AND F. F. RUNDLE

With Experimental Data by

H. B. COLLARD, F. H. MILLS, and F. F. RUNDLE

(From the Westminster Hospital Medical School and the Bernhard Baron  
Research Laboratories of the Royal College of Surgeons)

*Introduction*

THE object of this paper is to report the results of an investigation of hepatic function in thyrotoxicosis. That considerable liver damage may occur in this condition is suggested by several independent pieces of evidence which do not seem to have received general recognition, perhaps because they have not yet been adequately correlated with the clinical manifestations of the disease.

Considering first the functional aspect, Cramer and Krause (1913) showed that the liver glycogen could be reduced to a mere trace by feeding fresh thyroid gland to rats or cats. This finding has been confirmed by Bösl (1928), Frazier and Frieman (1935), and Coggeshall and Greene (1933). On the clinical side, an impairment of the tolerance for glucose has been recognized for many years as of frequent occurrence in hyperthyroidism. This is presumably related, at least in part, to the above observation, but the complicating effects of the insulin mechanism have prevented clear deductions from being drawn as to hepatic function.

Laevulose and galactose, whose metabolism is more or less independent of insulin, have been used in an effort to overcome this difficulty, but the methods of estimation of these sugars as distinct from the total blood-sugar have only recently been worked out, and this no doubt accounts for some of the contradictory reports. Lichtman (1932), for example, found that the urinary excretion of galactose was normal, whereas Althausen and Wever (1937), who were apparently the first to estimate blood-galactose in hyperthyroidism, produced acceptable evidence of impaired function. The former technique admittedly gives many negative results, even in patients with known liver damage. Althausen and Wever determined the blood-galactose at intervals up to thirty minutes after the ingestion of 40 gm. of the sugar. From the present study, however, it is evidently preferable to extend this period to at least two hours, and a preliminary report of the striking results which

<sup>1</sup> Received May 4, 1940.

can be demonstrated in severe thyrotoxicosis by this method has already been made by one of us (Maclagan, 1940).

Positive results have also been claimed with other functional tests, e.g. van den Bergh and bromsulphalein excretion test (Youmans and Warfield, 1926; Heilmeyer, 1931; Lichtman, 1932; Maddock, Collier, and Pedersen, 1936), hippuric acid test (Boyce and McFetridge, 1938; Lichtman, 1938; Bartels, 1938). The rarity of jaundice in hyperthyroidism suggests that tests based on the excretory function of the liver are probably unsuitable for the present purpose.

Secondly, the autopsy findings have yielded significant results to workers who have made a special search for them. For example, Beaver and Pemberton (1933) reported the occurrence of acute hepatic lesions, necrosis, and fatty degeneration in over 90 per cent. of cases. Simple liver atrophy and varying degrees of monolobular cirrhosis were even more conspicuous changes. These degenerative lesions have generally been ascribed to the direct effect of the thyroid toxæmia (Rössle, 1933; Haban, 1933; Wegelin, 1936), although the possible influence of the thyrotrophic hormone should not be overlooked. The high incidence of hepatic damage in thyrotoxicosis is possibly connected with the fact that the liver is concerned with the decomposition and excretion of the thyroid hormone (Elmer and Luczynski, 1933; Elmer, 1938).

Finally, Moon's (1936) survey of the association of hepatic cirrhosis and thyroid disease in the United States of America provides very suggestive evidence. Those States having the highest death roll from thyroid disease have also the highest from cirrhosis of the liver, and vice versa. Similarly, he showed that in Europe the highest incidence of cirrhosis is in Switzerland, where the high incidence of goitre is well known.

#### *Methods*

In the present investigation, hepatic function in Graves' disease has been studied by a modified technique for determining the galactose tolerance, full details of which appear elsewhere (Maclagan, 1940). Forty grammes of galactose are administered orally and the blood-galactose estimated half, one, one and a half, and two hours afterwards. A post-absorptive curve can thus be plotted (Fig. 1A). The peak of the curve did not exceed 80 mg. of blood-galactose per 100 c.c. in 50 normal persons, and normal curves were also seen in diabetes mellitus. A reliable and convenient criterion for comparing the galactose tolerance in different subjects is the 'galactose index'. This term is used to denote the sum of the blood-galactose values, expressed in mg. per 100 c.c. at half, one, one and a half, and two hours after the ingestion of the test dose. The upper normal limit for the galactose index is 160. The average normal value is 68, and the standard deviation is 39.3.

The basal metabolic rates were all estimated by one of us (N. F. M.) by the graphic Benedict-Roth method, substantially as described by Beaumont and

Dodds (1939), and Robertson (1938). The tests were performed in the metabolism room on the fasting patient after a preliminary rest of at least forty-five minutes, and the patients were familiarized with the technique by having a trial test performed on the preceding day. Two ten-minute records were taken which usually agreed closely, but if they failed to do so either a third record was made or the test was repeated on another day. The Boothby and Sandiford (1929) standards were used in place of those given by the authors mentioned above.

The material consisted of 41 patients with definite clinical thyrotoxicosis. Borderline or doubtful cases were excluded from this study, and the diagnosis was made on clinical grounds by one of us (F. F. R.). None of the patients was jaundiced.

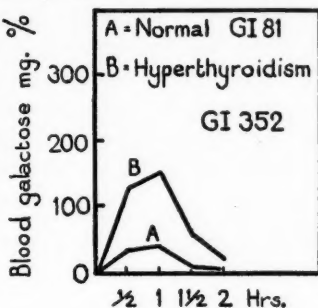


FIG. 1.

### Results

Fig. 1 shows a typical normal curve from a student and a typical abnormal curve from a patient with Graves' disease. In the former case, the maximum blood-galactose value was 39 mg. per 100 c.c., in the latter the corresponding figure was 147. The value for the galactose indices were 81 and 352 respectively. The galactose tolerance was, therefore, clearly impaired in the patient with thyrotoxicosis. Both curves are roughly symmetrical, the peaks being at the one-hour period. This is by no means invariably the case, and the maximum value may occur half or one and a half hours after administration. Consequently, observations of the blood-galactose level for only thirty minutes after ingestion of the test dose may give an erroneous impression of the true tolerance, as is shown in the following cases:

TABLE I

*Comparison of Thirty-minute Reading with Maximum Value of Blood-galactose Curve and Galactose Index*

Case No.	Diagnosis.	Blood-galactose in mg. per 100 c.c. at 30-min. period.	Maximum value of blood-galactose curve.	Galactose Index.	Comment.
1	Control	73	73 (at 30 min.)	150	Tolerance normal
2	Control	72	72 (at 30 min.)	86	Tolerance normal
3	Control	45	60 (at 60 min.)	126	Tolerance normal
4	Control	43	68 (at 60 min.)	132	Tolerance normal
5	Severe thyro-toxicosis	33	112 (at 60 min.)	250	Tolerance impaired
6	Severe thyro-toxicosis	44	105 (at 90 min.)	312	Tolerance impaired
7	Severe thyro-toxicosis	47	89 (at 60 min.)	215	Tolerance impaired

Fig. 2 gives the galactose indices in the 41 patients with thyrotoxicosis shown in comparison with the results obtained in normal persons and also in toxic and obstructive jaundice. It is interesting to compare the three types of liver damage shown in this figure:

1. Jaundice with normal glycogenic function (obstructive jaundice).
2. Jaundice with impaired glycogenic function (toxic jaundice).
3. Impaired glycogenic function without jaundice (hyperthyroidism).

Thirty out of the 41 cases of thyrotoxicosis showed definite impairment of

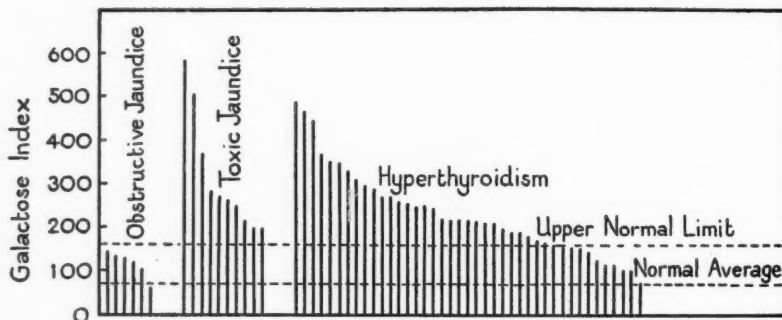


FIG. 2.

glycogenic function of a degree comparable with that seen in toxic jaundice; even the remaining 11 all gave results above the normal average.

Table II shows the effect of a period of fourteen days' rest in bed and iodine therapy on the basal metabolic rate and galactose index in a group of five patients with thyrotoxicosis, none of whom had ever taken iodine previously.

TABLE II

*Effect of Fourteen Days' Rest and Iodine Therapy on the Galactose Index and Basal Metabolic Rate*

Patient No.	(Pre-iodine)		(Post-iodine)	
	G.I.	B.M.R. %	G.I.	B.M.R. %
1	218	+50	241	+16
2	215	+47	241	+34
3	292	+58	333	+31
4	273	+60	204	+11
5	472	+47	398	+38
Averages	291	+52	283	+26

It will be seen that while the basal metabolic rate decreased in each case, the galactose indices showed little significant change, the averages before and after iodine being nearly identical. The patient in whom the galactose index decreased most with rest and iodine is of some interest (No. 5). The pre- and post-iodine values were 472 and 398 respectively. Thyrotoxicosis was complicated by auricular fibrillation with rapid heart-rate. There was



no oedema, but some degree of cardiac failure and hepatic congestion was presumably present on admission. The ventricular rate gradually subsided during the period of rest and iodine therapy. Therefore some improvement in liver function may have been produced by general treatment altogether apart from its effect on the thyrotoxic state. From these observations it appears that while rest and iodine usually lower the basal metabolic rate markedly, they are without significant effect on the galactose index in uncomplicated cases.

Table III shows the effect of subtotal thyroidectomy on the galactose index and basal metabolic rate in 16 patients in which pre- and post-

TABLE III

*Effect of Thyroidectomy on the Basal Metabolic Rate and Galactose Index*

Grade of thyrotoxicosis.	B.M.R. pre-op. %	B.M.R. post-op. 14 days. %	G.I. pre-op.	G.I. post-op. 14 days.	G.I. post-op. 6 weeks.	G.I. post-op. 12 weeks.
1. Severe	+31	+18	333	268	92	
2. "	+52	-14	312	72		
3. "	+63	+6	263	70		
4. "	+53	+12	249	116		
5. "	+73	+7	213	106		
6. "	+20	-10	211	223	175	174
7. "	+11	+5	204	184	103	
8. "	+42	-1	199	161		
9. "	+39	+1	112	82		
10. Moderate	+32	-3	255	106		
11. "	+16	+3	241	130		
12. "	+34	+1	241	51		
13. "	+2	-2	197	112		
14. "	+14	-9	192	—	79	
15. "	+57	-4	156	172		
16. Mild	+41	-13	179	154		

operative estimations were made. In some patients the basal metabolic rate reading before operation is low owing to the fact that the pre-operative value was usually obtained within a few days of subtotal thyroidectomy when a full iodine response had occurred.

Thyroidectomy is seen to produce a striking decrease in both the basal metabolic rate and the galactose index. The return to normal values was more prompt and complete in the case of the basal metabolic rates. Moreover, of the four patients in whom the galactose index was still raised two weeks after operation, only one gave a high value (175) six weeks after operation. A subsequent estimation twelve weeks after operation resulted in a reading of 174, so that a permanent slight elevation in the value may have been present in this case (No. 6).

Table IV shows the results obtained in five cases in which the test was done at a more remote period after thyroidectomy. In all patients thyrotoxicosis had been severe, but there was then no evidence clinically of any metabolic disturbance at the time of the tests.

TABLE IV  
*Remote Post-operative Galactose Index*

Case No.	Pre-operative clinical state.	Interval after sub-total thyroidectomy.	B.M.R.	Galactose Index.
1	Severe thyrotoxicosis	12 months	+ 2	180
2	Severe thyrotoxicosis associated with jaundice	2 years	+ 4	173
3	Severe thyrotoxicosis	18 months	- 16	157
4	Severe thyrotoxicosis	12 months	—	90
5	Severe thyrotoxicosis, congestive failure with oedema, and liver enlargement	12 months	+ 4	86

Although these values are not much above normal limits, they are all well above the average (68), and their own average is about twice this figure.

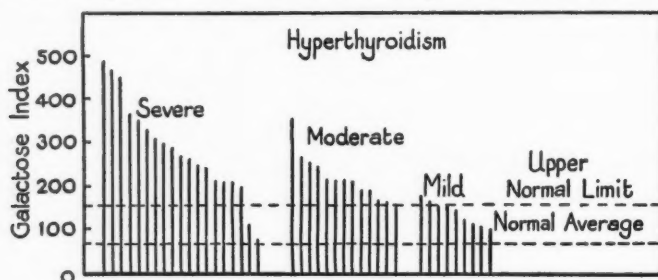


FIG. 3.

Their mean (137) is certainly significantly different from the normal mean, as shown by Fisher's (1932) 't' test, which gives a probability well below 0.01 ( $t = 3.77$ ). These figures should therefore be interpreted as indicating slight residual liver damage in this group of patients.

In an attempt to determine whether the actual height of the galactose index was related to the severity of the clinical condition, the 41 patients were grouped according to whether the thyrotoxicosis was clinically severe, of moderate intensity, or mild. Such grading cannot, of course, be a matter of exactitude, but it can be done with sufficient accuracy for the purpose of the present discussion by reference to such features as the extent of the loss of weight, the degree of myasthenia, excitability, and tachycardia. The patients were all examined with this object in view by one of us (F. F. R.).

Fig. 3 and Table V shows the results of such grouping. Within the individual group the cases are arranged in descending order of the galactose indices.

TABLE V

Grade of thyrotoxicosis.	No. of cases.	Mean B.M.R.	Mean G.I.	Standard error.	Standard deviation.	Per cent. of cases with G.I. of		
						over 160.	160 to 68.	below 68
Severe	19	+ 52%	285	25.2	110	84.5	13	2.5
Moderate	13	+ 37%	220	14.8	53.3	87	13	< 0.5
Mild	9	+ 29%	137	9.2	27.4	15	84.5	0.5
Normal	50		68	5.55	39.3	—	44	56

It will be seen that there is a clear general relationship between the clinical grade of the thyrotoxicosis, the basal metabolic rate, and the galactose index. In the severe and moderate grades a raised galactose index was a fairly constant finding, occurring in 29 out of the 32 cases. In the mild group while only two out of the nine cases gave values above normal limits, the remaining seven were in the upper normal range (all above 100) and the mean value of this group (137) differs quite significantly from the normal mean (difference =  $69 \pm 10.8$ ). There is therefore satisfactory evidence of hepatic dysfunction even in the mild group taken as a whole, although only a proportion of the results were actually above normal limits. Since there was no case with a galactose index below the normal average (68) it would appear that such a result must be very uncommon in hyperthyroidism.

A further statistical analysis of the material has been made in the last three columns of Table V, which show the percentages of cases which should fall between certain limits, assuming a normal distribution of values. The figures are calculated from the standard deviations in the cases of thyrotoxicosis, but the observed results have been preferred for the normal subjects. These calculations confirm the conclusions given above, particularly with respect to the rarity of results below 68 in hyperthyroidism. One peculiarity which requires comment is the greater probability (2.5 per cent.) of such results in severe as opposed to moderate or mild grades (0.5 per cent.). A possible explanation of this lies in the absence in our material of mild cases with short histories which would no doubt be associated with low results; such patients do not often present themselves for treatment. About 85 per cent. of severe or moderate cases, and about 15 per cent. of mild cases, should give results above normal limits.

In spite of the clear general relationship between the clinical severity of the disease, the basal metabolic rate, and the galactose index, there is considerable overlapping in individual cases. Thus some of the patients with moderate thyrotoxicosis are seen to have had higher readings than others in whom the disease was severe. Individual variations in the age and duration of thyrotoxicosis appear to be of importance in this connexion. For example, both patients in the severe group in whom the index was within normal limits were adolescent and had short histories (two months and three months). Further, all four patients in the moderate group in whom the index was 250 or more had histories of two years or longer. While it seems certain that some relationship exists between the duration of the disease and the degree of impairment of liver function, the uncertainty of the former factor prevents the establishment of any mathematical correlation between the two.

Fig. 4 shows the result of plotting the galactose index against the 'pre-iodine' basal metabolic rate in 33 patients with clinically definite thyrotoxicosis. Cases in which only 'post-iodine' basal metabolic rates were available have been excluded from this diagram as far as possible. The correlation is significant, but not very close (correlation coefficient 0.417).

Here again the lack of a more complete correlation is no doubt due to variations in the age of the patient and the duration of the disease. For example, the patient with basal metabolism +56 and galactose index of only 75 was a girl aged 13 years with a short history. It may be noted here that if the 'post-iodine' basal metabolic rates are included, there is no significant correlation between the basal metabolic rates and galactose indices in the 41 patients with definite hyperthyroidism. This is not unexpected in view of the difference in the effects of iodine on the basal metabolic rate and galactose index referred to above.

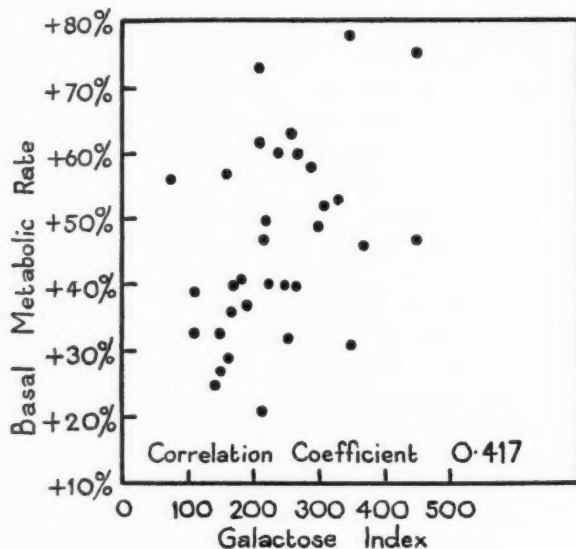


FIG. 4.

*Experimental Data* (by H. B. Collard, F. H. Mills, and F. F. Rundle)

The effect of thyroxine on galactose tolerance was also investigated in the following experiments on rabbits, in which the test was done before and after a period of daily subcutaneous administration of the drug. The technique was similar to that described above, except that the galactose was given intravenously in a 10 per cent. solution. The shape of the curve was consequently different, but the term 'galactose index' has been used in the same sense, i.e. as the sum of the four blood galactose values at half, one, one and a half, and two hours after injection of the test dose (2 gm. of galactose per kg. of body-weight).

Fig. 5 shows the results obtained in 10 normal rabbits contrasted with five of the same animals after thyroxine therapy. The numbers on the curves refer to Table VI which summarizes the data. It is evident that all the five thyroxine-treated animals gave results well outside the normal range, and all showed substantial increases on their respective control

figures. The mean galactose index of the treated animals (527) is about double that of the untreated (215), and it is obvious that a notable impairment of liver function has been demonstrated in these experiments.

The five thyroxine treated rabbits were finally killed and the livers were examined. Although normal macroscopically, each one showed definite histological evidence of degeneration leading to acute and subacute necrosis. The changes were focal in type and affected principally the central and periportal zones.

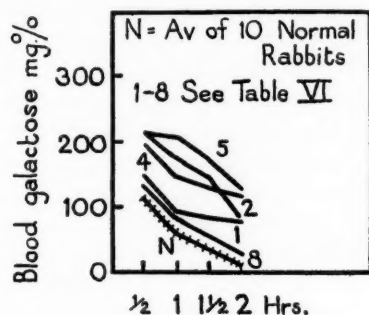


FIG. 5.

TABLE VI

*Effect of Thyroxine Subcutaneously on the Galactose Index in Rabbits*

Rabbit No.	G.I. untreated.	Daily Thyroxine.	G.I. after treatment.	Rise in G.I.
1	293	1 mg. for 6 days	408	+115
2	282	1 mg. for 17 days	618	+336
3	263	—	—	—
4	255	1 mg. for 11 days	574	+319
5	215	2 mg. for 13 days	726	+511
6	177	—	—	—
7	171	—	—	—
8	168	2 mg. for 6 days	310	+142
9	165	—	—	—
10	164	—	—	—
Averages	215		527	+285

### Discussion

The utility of estimations of the galactose tolerance in patients with thyrotoxicosis may be discussed under the following headings:

(1) *The nature of the function tested.* The galactose tolerance depends essentially upon hepatic glycogenesis. As pointed out in the introduction, this is the liver function which is particularly impaired in thyrotoxicosis, and the test therefore aims at revealing the typical disorder of the liver in this disease. Glycogen has frequently been stated to be of importance in protecting the liver-cells from injury. For example, Davies and Whipple (1919) showed experimentally that a diet rich in carbohydrate given in the days

preceding chloroform anaesthesia exerts a marked protective action and lessens the evidence of liver necrosis from chloroform poisoning. It is possible, therefore, that the toxic effect of the thyroid hormone on the liver is connected with its action in interfering with glycogenesis.

(2) *The pathological significance of the galactose index.* The data suggest that, when the galactose index is very high, structural liver damage is probably present. The fact that histological lesions have been found in such a high percentage of cases *post mortem*, and that a raised galactose index also occurs with striking frequency in severe and moderate cases, provide suggestive evidence. Only one patient of the present series was examined *post mortem*. Thyrotoxicosis had been severe. The basal metabolic rate was +75 per cent. and the galactose index 448. Histologically there was periportal and focal necrosis and marked generalized liver atrophy. Moreover, in the rabbits injected with thyroxine a raised galactose index was associated with focal necrosis of the liver-cells in all the five animals examined. The five patients with past severe hyperthyroidism (Table IV) also give confirmatory evidence on this point, for they still showed evidence of impaired function at periods up to two years after the original condition had been cured, suggesting the possibility of permanent hepatic damage.

When the galactose index is only moderately raised, our data do not show whether the change is merely a functional one or whether organic lesions are also present. The fact that normal limits were usually regained in fourteen days favours the former explanation, but there was one case which still gave a reading of 175 twelve weeks after thyroidectomy (Case No. 6; Table III; pre-operative reading 260). The fact that the iodine therapy has little or no effect on the galactose index also suggests the possibility of an organic change.

With regard to the cause of the liver dysfunction, our results suggest that it is probably a direct consequence of the thyroid toxæmia, and is not usually produced by over-secretion of thyrotrophic hormone. This follows from the prompt return to normal after thyroidectomy in most cases, and from the striking results produced in rabbits by thyroxine administration. There is, however, considerable evidence that excess of thyrotrophic hormone can produce liver damage (Best and Campbell, 1936; Mukerji and Guha, 1938), and this possibility cannot be excluded in those cases showing impaired function at considerable intervals after thyroidectomy (see Table IV, and patient No. 6, Table III).

(3) *The clinical significance of the galactose index.* It is our suggestion that the test provides the equivalent of an additional physical sign in hyperthyroidism which has certain advantages over some of the other signs. Firstly it is relatively unaffected by iodine therapy, and secondly it is capable of quantitative measurement in a sense which has a definite relationship to the severity of the disease. It is in fact the only sign which fulfils both these requirements. While no one sign in hyperthyroidism is either absolutely constant or absolutely specific, it would appear from our data that this particular type



of liver dysfunction occurs about as frequently as loss of weight,<sup>2</sup> while other conditions which might cause liver damage can usually be eliminated on clinical grounds without difficulty.

A high galactose index (over 160) therefore affords confirmation of the diagnosis and provides objective evidence of liver damage which is quite undetectable clinically. Some indication of the possible importance of hepatic derangement in the severer degrees of thyrotoxicosis and of the uncertainty which attends its detection is given in Lahey's (1935) statement: 'While I cannot undeniably establish the fact that the deaths associated with excessive hyperthyroidism are largely liver deaths, I have personally for a number of years, been convinced of this fact and with widening experience am more and more sure of it.' This appears extremely probable in view of the role of the liver in the destruction and excretion of thyroxine referred to above, with the possibility of a vicious circle developing—excess thyroxine, liver damage, failure to destroy thyroxine, further excess of thyroxine. A very high reading (say over 400) may be therefore taken as indicating the necessity of very careful surgical management, and we may recall that the only patient who died from thyroid crisis in this series had a galactose index of 448 before operation.

A high normal result (68 to 160) while not absolutely excluding hyperthyroidism, was found either with a very mild grade or with a very short duration of symptoms. In either case, it indicates that perhaps the most essential link in the body's chain of defences to thyroxine is not grossly impaired, and suggests that radical treatment is not of great urgency. If the doctor has any belief in the efficacy of medical treatment, these are presumably the cases in which it is particularly appropriate, always assuming that other considerations, such as cardiac condition, local factors, &c., are favourable.

A low normal galactose index (0 to 68) would appear to exclude hyperthyroidism, since we did not observe such values in a single case, and statistical analysis of the results indicates that they would rarely occur. In border-line or doubtful cases, the test may be used to advantage in combination with the basal metabolic rate. Used alone, the latter may raise difficult problems of interpretation, particularly after iodine therapy when normal readings are not uncommon even in cases of definite hyperthyroidism, or where the reading is only slightly raised. In such cases the finding of a low normal galactose index would tend to exclude thyrotoxicosis, while a high reading would support the diagnosis. A proportion of these cases will, of course, give only the inconclusive high normal result. It is hardly necessary to emphasize the importance or the difficulty of this type of case as a clinical problem at a time when so many patients arrive at hospital after an unsuccessful course of iodine treatment which may sometimes vitiate the diagnostic value of the basal metabolic rate estimation.

<sup>2</sup> Out of the 41 cases 33 gave a history of significant loss of weight, and 30 had galactose indices over 160.

*Summary*

1. Liver function has been studied by means of a modified galactose tolerance test in 41 patients with hyperthyroidism.

2. Out of the 41 patients 30 showed definite impairment of liver function, and the remaining 11 all gave results in the upper normal range (galactose index above 68).

3. Clinical grading of the cases into three groups, severe, moderate, and mild, showed a definite relationship between the galactose index and the severity of the thyrotoxicosis. There was also a significant correlation between the galactose index and the basal metabolic rate in untreated patients.

4. Rest and iodine therapy had little effect on the galactose index, but thyroidectomy produced a prompt fall to normal values in most cases. Some degree of residual hepatic impairment was, however, demonstrated in a small group of patients studied at long intervals after thyroidectomy for severe hyperthyroidism.

5. Experiments on rabbits are reported in which the daily subcutaneous administration of thyroxine for periods up to seventeen days produced a marked impairment of tolerance to galactose injected intravenously. The livers of these animals also showed severe focal necrosis when examined histologically.

6. These results are discussed from the clinical, diagnostic, and pathological standpoints.

For access to clinical material, we are indebted to the honorary staff of the Westminster Hospital, the London County Council, and the staff of the Thyroid Clinic at New End Hospital, Hampstead. The animal experiments were performed in the Bernhard Baron Research Laboratories of the Royal College of Surgeons under the direction of Dr. J. Beattie, for whose help and criticism we are also grateful. Two of us (N. F. M. and F. F. R.) are indebted to the John Burford Carlill Research Fund for financial assistance. The work was done during the tenure of a MacKenzie Mackinnon Scholarship, Royal College of Surgeons, by H. B. Collard, and a Leverhulme Scholarship, Royal College of Surgeons, by F. H. Mills.

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## POSTSCRIPT

WHILE this paper was in the press, two papers have appeared (Althausen, 1939; Althausen, Lockhart, and Soley, 1940) giving the results of a similar investigation on galactose tolerance in hyperthyroidism, in which the blood-galactose was estimated at thirty and sixty minutes after an oral dose of 40 gm. of galactose. Although these workers obtained results very similar to our own in hyperthyroidism, we are not in agreement with their normal figures or with their interpretation of the results.

Firstly, they regard 30 mg. per 100 c.c. as the normal maximum blood-galactose during the test in '21 volunteers'. In our series the maximum was not always reached at one hour, but even up to this time we have seen values up to 63 in 20 normal male medical students and up to 81 in 30 'normal' out-patients (MacLagan, 1940). The *average* maximal value for our 50 normal subjects was 32. Their method of estimating the blood-galactose appears to be similar to ours, but the details given in the above papers are rather brief, and do not include reference to the analysis of a standard galactose solution as a check on the yeast, a point to which we attach some importance.

Secondly, the authors describe the test as 'a test of intestinal absorption' and do not discuss the possibility of liver damage in thyrotoxicosis. Their principal justification for this appears to be the results of intravenous galactose tests on 10 patients with Graves' disease which were said to be identical with similar tests performed on 11 normal subjects. No further details are given. Independent evidence of increased intestinal absorption in animals treated with thyroxine was also adduced. As against this we have our intravenous galactose tolerance experiments on rabbits treated with

thyroxine, and a considerable amount of collateral evidence of liver damage in hyperthyroidism from the clinical and pathological aspects. It is, of course, possible that both liver damage and increased intestinal absorption are concerned with the high curves seen in hyperthyroidism, but further work with a combination of oral and intravenous methods would appear to be the only way to elucidate this problem.

Fortunately the clinical value of the test is not necessarily affected by these speculations as to its mechanism, and our results in thyrotoxicosis are in substantial agreement with those of Althausen, Lockhart, and Soley (1940), who indeed describe the test as being as reliable as the basal metabolic rate in the diagnosis of this condition. Thus 129 out of their 130 cases, and all of ours, gave maximal blood-galactose values over 30 mg. per 100 c.c. As noted above, this value corresponds to our average normal, but to Althausen's highest normal figures, so that our interpretation of these findings differs from his. Thirty-three per cent. of his cases and 73 per cent. of ours had maximal blood-galactose values above our upper normal limit (80 mg. per 100 c.c.).

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## THE ACTION OF PARASYMPATHETIC-MIMETIC DRUGS IN ASTHMA<sup>1</sup>

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PILOCARPINE has been used for testing asthmatics (Alexander and Paddock, 1921), but as it produces sweating and salivation rather than bronchospasm it is not very satisfactory; of the parasympathetic-mimetic drugs the stable choline esters are more useful, and of these acetyl- $\beta$ -methylcholine ('mecholy'l', Merck) is particularly interesting in view of its action on the bronchi. Mecholy'l mimics parasympathetic stimulation and has muscarine-like actions similar to those of acetylcholine, but is more stable. It may be administered by subcutaneous or intramuscular injection, by the mouth, by instillation into the conjunctival sac, and by ionization. The usual dose by subcutaneous injection is from 10 to 25 mg., but for the purpose of this investigation the dose has been kept low, and not more than 10 mg. given as a rule; if no response with this dose was obtained a second test with 20 mg. was made.

*Effect of mecholy'l in asthma.* Villaret, Vallery-Radot, Justin-Besançon, and Claude (1934) tested 15 cases of asthma with mecholy'l and found asthma-like attacks produced in every case. They used larger doses and gave from 20 to 40 mg. by subcutaneous injection. Starr, Elsom, and Reisinger (1933) also observed asthma-like attacks in asthmatics after the administration of mecholy'l. The following is an example of the type of response to an injection of mecholy'l which may be observed in an asthmatic subject:

The patient, a woman aged 32 years, had suffered from periodic asthma for fourteen years, with periods of freedom lasting up to three years. The last attack had occurred two months previously, but some wheeziness always occurred in the mornings. The asthma was 'infective' in origin. The lungs at the time of the test were clear of adventitious sounds; 10 mg. of mecholy'l were injected subcutaneously into the arm (zero time). At two minutes the face flushed and there was slight lachrymation. At five minutes rhonchi began to appear over both lungs. There was a fall of blood-pressure and the respiratory rate increased from 12 to 24. Slight sweating and salivation were observed. At eight minutes the chest felt tight to the patient and coughing occurred. At twelve minutes the chest felt very tight to the patient and there was wheeziness. Numerous rhonchi could then be heard over both lungs. At fourteen minutes there was audible wheezing and the rhythm of the respirations was similar to that observed during an attack of

<sup>1</sup> Received May 22, 1940.

asthma. At sixteen minutes adrenaline hydrochloride, 7 minims of a 1 in 1000 solution, was injected subcutaneously. Two minutes later the patient felt easier and wheezing was disappearing; six minutes after the injection of adrenaline she felt normal again.

The attack produced by mecholyl is indistinguishable from a spontaneous attack of asthma and patients say that they experience the same sensations. Observations on the effect of mecholyl have been repeated on a series of 28 cases of asthma; the series includes cases of different severity and type (see Tables I and II). All patients were adults with the exception of one case, a boy aged 12 years; children are usually unsuitable subjects as they become unduly restless and alarmed by the side-effects. The test should

TABLE I

*Cases of Asthma Grouped According to the Severity of Attacks\**

Group I . . . .	1 case	Group IV . . . .	11 cases
Group II. . . .	6 cases	Group V. . . .	1 case
Group III . . . .	5 cases	Unclassified . . . .	4 cases

\* Classification suggested by the Asthma Research Council (Bray, 1937). Groups I and II include constant types of asthma, Groups III and IV periodic types. Group V includes patients who have been free from asthma for at least two years.

TABLE II

*Cases of Asthma Classified According to the Main Aetiological Factor*

Allergic . . . .	12 cases	Psychic factor . . . .	2 cases
Infective. . . .	9 cases	Unclassified . . . .	2 cases
Nasal factor . . . .	3 cases		

not be undertaken indiscriminately, even in adults, as the reaction at times may be very marked and cyanosis and symptoms of collapse may occasionally supervene. No untoward effects, however, have been observed in the 66 cases in which the test was carried out.

Asthmatic subjects almost invariably respond to an injection of mecholyl by the appearance of respiratory symptoms. The symptoms may vary in intensity from a transient wheeze and the appearance of a few rhonchi to the development of a severe seizure with marked asthmatic breathing. In the present series of 28 cases, only eight failed to develop respiratory symptoms; of these, two cases reacted very slightly to 10 mg. of mecholyl and the test was inconclusive; three other cases, all slight reactors, failed to develop respiratory symptoms with 10 mg. of mecholyl, but developed definite wheeziness when re-tested with 20 mg.; only one case failed to develop chest symptoms, though the general reaction was marked. Two other cases failing to show respiratory symptoms were cases of hay asthma, and the test was carried out in the winter (see Table III).

The attack resembling asthma produced by mecholyl does not appear as quickly as other symptoms of vagal stimulation, and usually signs and symptoms of asthma are noted five to ten minutes after the injection; in some cases the delay in onset of respiratory symptoms may be even more



marked; in one case an asthmatic attack developed fifteen minutes after the injection and in another case twenty-one minutes afterwards. Flushing of the face and some degree of salivation, lachrymation, and sweating usually appear within one and a half to two minutes after the injection. A distinct phasic variation is noted in some cases, the intensity of both the respiratory

TABLE III  
*Response of Asthmatic Subjects to Mecholyl*

Case No.	Type.	Group.	Dose of mecholyl. mg.	Respiratory symptoms.	General reaction.
1	?	3	10	slight	marked
2	allergic	4	10	marked	marked
3	allergic	4	10	slight	marked
4	allergic	?	10	moderate	moderate
5	allergic	2	10	moderate	slight
6	allergic	3	10	moderate	moderate
7	allergic	4	10	none	slight
8	allergic (pollen)	4	10	none	moderate
9	allergic (pollen)	4	10	none	moderate
10	allergic	1	10	marked	marked
11	allergic	4	10	marked	slight
12	allergic	?	5	moderate	moderate
13	allergic	5	10	moderate	moderate
14	infective	3	10	moderate	slight
15	infective	3	10	moderate	marked
16	infective	4	10	marked	moderate
17	infective	2	10	marked	marked
18	infective	?	10	moderate	marked
19	infective	4	10	marked	marked
20	infective	2	10	none	marked
21	infective	4	10	moderate	marked
22	infective	2	10	none	slight
			20	moderate	marked
23	nasal polypi	2	10	marked	slight
24	deflected septum	4	10	none	slight
25	nasal polypi	3	10	marked	marked
26	?	4	10	slight	slight
27	psychogenic	?	10	none	moderate
			20	moderate	marked
28	psychogenic	2	10	none	slight
			20	marked	marked

symptoms and of other signs of parasympathetic stimulation waxing and waning over periods of several minutes.

*Effect of mecholyl in control subjects.* The control subjects have been divided into two groups, A and B. Group A included 10 hospital patients suffering from non-respiratory diseases. Group B was composed of nine medical students. All patients in group A failed to develop respiratory symptoms except a man, 60 years of age, suffering from pernicious anaemia and subacute combined degeneration of the cord, in whom a few rhonchi appeared after the mecholyl injection; he was probably also a bronchitic as rhonchi had been heard over his chest a few days before the test was carried out. Two cases of Addison's disease failed to develop respiratory symptoms. In one there was definitely increased sensitivity to mecholyl, and a 2 mg.

dose, which usually has no effect in a normal subject, gave rise to distinct flushing and sweating.

All nine medical students comprising group B failed to develop respiratory symptoms after mecholyl. Tightness of the chest was noted by some, but

TABLE IV  
*Response of Non-asthmatic Subjects to Mecholyl*  
(Three cases of secondary asthma have also been included)

Case No.	Nature of case.	Dose of mecholyl. mg.	Respiratory symptoms.	General reaction.
1	Medical student	10	none	slight
2	Medical student	10	none	marked
3	Medical student	10	none	moderate
4	Medical student	10	none	moderate
5	Medical student	10	none	marked
6	Medical student	10	none	moderate
7	Medical student	10	none	marked
8	Medical student	10	none	moderate
9	Medical student	10	none	marked
10	Arthritis	10	none	slight
11	P.M.A.	10	none	slight
12	Cholecystitis	5	none	moderate
13	Neurosis	10	none	moderate
14	P.M.A.	10	none	slight
15	P.M.A.	10	none	slight
16	Rheumatic fever	10	none	moderate
17	Pernicious anaemia	10	slight	moderate
18	Addison's disease	5	none	moderate
19	Addison's disease	2	none	moderate
20	Pneumonia 1 mth. before	10	none	moderate
21	Pneumonia 1 mth. before	10	slight	marked
22	Bronchial carcinoma	10	none	slight
23	Pulmonary tuberculosis	10	none	marked
24	Pulmonary tuberculosis	10	none	marked
25	Pulmonary tuberculosis	10	none	marked
26	Cardiac asthma	20	none	marked
27	Cardiac asthma	10	slight	slight
28	Bronchiectasis	10	none	marked
29	Bronchiectasis	5	marked	moderate
30	Bronchiectasis	10	none	slight
31	Bronchiectasis and asthma	10	marked	marked
32	Bronchiectasis	10	slight	marked
33	Bronchiectasis and asthma	10	marked	moderate
34	Bronchiectasis	10	slight	marked
35	Bronchiectasis	10	slight	marked
36	Bronchiectasis	10	slight	marked
37	Bronchiectasis	10	none	moderate
38	Fibrinous bronchitis and asthma	10	marked	marked

this was never associated with wheeziness, asthmatic breathing, or the appearance of rhonchi (see Table IV). Starr, Elsom, and Reisinger (1933), and Villaret, Vallery-Radot, Justin-Besançon, and Claude (1934) also observed in a number of cases that normal subjects did not develop chest symptoms after a mecholyl injection.

*Effect of mecholyl in other respiratory diseases.* This group included 10 cases of bronchiectasis, two cases convalescent from pneumonia, a case of fibrinous bronchitis, a case of bronchial carcinoma, and three cases of active pulmonary

tuberculosis. All the cases of bronchiectasis had been confirmed by bronchography; in six cases the dilatation was saccular, in three cases tubulosaccular, and in one case early tubular. Only one case gave a history of allergy, the patient being a dustman and giving a strong positive intradermal test to dust. Eosinophilia was also present in the sputum, and the patient suffered from asthma. Another patient suffered from asthmatic attacks, while in two cases some wheeziness and tightness of the chest occurred with recurrent attacks of bronchitis. In the remainder there was no history of either wheeziness or asthma. A definite respiratory attack after an injection of mecholyl was noted only in those cases of bronchiectasis which were associated with asthma, while patients with bronchiectasis, but not suffering from wheeziness or asthma, did not develop chest symptoms, or the symptoms were very slight indeed. There was only one exception, a case of saccular bronchiectasis, in which, however, 30 per cent. of eosinophils were present in the sputum.

A patient with fibrinous bronchitis and associated asthmatic attacks developed an extremely severe attack of asthma after an injection of 10 mg. of mecholyl, and the attack persisted even after an injection of 1/100 grain of atropine and of 7 minims of adrenaline solution. Two patients convalescent from an attack of pneumonia which had occurred a month previously were tested with mecholyl; one developed very slight chest symptoms. A patient with an oat-celled carcinoma of the left upper lobe bronchus and paralysis of the left vocal cord, but not complaining of either asthma or wheeziness, was tested with mecholyl, but did not develop an attack of asthma.

Three cases of active pulmonary tuberculosis with positive sputum tests did not develop respiratory symptoms after mecholyl. All three patients reacted strongly with general symptoms of parasympathetic stimulation and showed marked flushing, lachrymation, salivation, and sweating; none of these patients had ever complained of either wheeziness or asthma. The failure of mecholyl to produce respiratory symptoms in these cases of pulmonary tuberculosis is in agreement with the clinical observation that, though tuberculosis and asthma are not antagonistic, the percentage of asthmatics with active tuberculosis is very low. Rackeman and Colmes (1929) found among 1,074 asthmatics active tuberculosis in only 13 cases and Sterling (1929), in 350 asthmatics, found that only five, or less than 1.5 per cent., had pulmonary tuberculosis with a positive sputum test.

*Effect of atropine, adrenaline, and ascorbic acid in controlling and inhibiting the action of mecholyl.* The action of mecholyl is rapidly controlled by atropine, and a subcutaneous injection of 1/100 gr. of atropine sulphate controls all the effects of parasympathetic stimulation, including the respiratory symptoms, in two to five minutes. Atropine also inhibits the action of mecholyl, and if a sufficient dose is given the inhibitory action may last several hours. In three cases the inhibitory action of atropine lasted three hours.

These observations, viewed in the light of current physiological conceptions, lend support to the view that the asthma-like attack produced by mecholyl is caused by stimulation of cholinergic nerves.

Adrenaline given hypodermically also controls the effects of mecholyl within two to seven minutes. Ascorbic acid in massive doses (500 mg.) injected intravenously has a similar action to adrenaline, although it is not so prompt and takes a few minutes longer to have effect.

Binet and Burstein (1939), utilizing the technique of the isolated and perfused lung in animal experiments, found that an injection of 50 mg. of ascorbic acid prevented the action of carbaminoyl-choline ('doryl', Merck). The following are two accounts of the action of ascorbic acid after the patients had received an injection of mecholyl.

*Case 1.* A subcutaneous injection of 10 mg. of mecholyl was given into the arm (zero time). At one and a half minutes there was flushing of the face and salivation. At three minutes the patient started to sweat and rhonchi began to appear in the lungs. At seven minutes the sweating became marked, wheeziness appeared, and numerous rhonchi could be heard over both lungs. At ten minutes 500 mg. of ascorbic acid were injected intravenously. Five minutes later the sweating had ceased, and ten minutes after ascorbic acid had been administered the respiratory symptoms had been completely controlled, and the lungs were clear of adventitious sounds.

*Case 2.* A subcutaneous injection of 20 mg. of mecholyl was given into the arm (zero time). At three minutes flushing of the face and a few rhonchi appeared in the chest. At four minutes sweating was noticeable. At seven minutes the patient complained of tightness of the chest, and numerous rhonchi were then audible over both lungs; sweating was profuse. Thereupon 500 mg. of ascorbic acid were injected intravenously. Three minutes later the chest felt easier, but rhonchi were still audible. Five minutes after the administration of ascorbic acid the chest was clear of adventitious sounds, and sweating had been completely controlled.

Both patients were asthmatic subjects. In the treatment of asthma with ascorbic acid reports have been contradictory, some authors claiming that vitamin C is of value (Hochwald, 1936; Epstein, 1936; Hagiesco, Bazavan, Criscota, and Cioranescu, 1938) while other observations tend to show that it has no beneficial effect (Hunt, 1938). Hochwald (1936) and Hagiesco, Bazavan, Criscota, and Cioranescu (1938), however, observed that when massive doses of ascorbic acid (300 to 1500 mg.) were injected intravenously, the attacks of asthma were definitely controlled, although the effect was slower than that of atropine and asthmolysin, and the return to normal of the respirations was gradual and sometimes incomplete. Ascorbic acid administered orally had no effect.

#### *Discussion*

The test with mecholyl does not help to differentiate different types of asthma, and examples of reflex asthma or those in which attacks are released psychogenically through nervous channels are not more susceptible to mecholyl than infective or allergic cases. The test may, however, be helpful in the diagnosis between true asthma and a respiratory neurosis, and especially hysterical hyperpnoea: bronchospasm occurs in the former case but not in the latter.

In cardiac asthma the test is not very helpful; two cases of left ventri-

cular insufficiency with nocturnal paroxysmal dyspnoea were tested; one did not develop respiratory symptoms but the other did: this may be explained by the fact that cardiac asthma due to left ventricular failure may also be associated with pulmonary stasis and asthmatic bronchitis, and the bronchial factor may interfere with the test.

Male, aged 50 years. Hypertensive heart disease with cardiac asthma. Blood-pressure 190/120. Mecholyl 20 mg. injected subcutaneously (zero time). At two minutes lachrymation and onset of sweating. Blood-pressure 150/90. At seven minutes marked sweating; at ten minutes marked sweating persisted, lachrymation, and salivation. Chest kept clear of adventitious sounds throughout the test and no asthmatic breathing was noted.

Male, aged 62 years. Hypertensive heart disease with myocardial degeneration and impaired conduction. Nocturnal paroxysmal dyspnoea. Blood-pressure 150/105. Emphysema. Some wheeziness occasionally. Mecholyl 10 mg. injected subcutaneously (zero time). At ten minutes chest felt very tight and some sibilant rales could be heard.

Increased susceptibility of the bronchi to mecholyl in asthma is observed both in the continuous and in the periodic type; it does not matter whether the attacks have been occurring frequently or not. The patient may have been free from attacks for months or even years and may still be susceptible; in this respect the dictum 'once an asthmatic always an asthmatic' proves true. In one patient there was a history of only one attack of asthma lasting a fortnight four years previously, but complete freedom since that time. Nevertheless he developed a definite asthmatic attack after mecholyl.

It is doubtful whether the attack produced artificially by an injection of mecholyl is identical with a spontaneous attack of asthma. Patients say that they experience similar sensations, and the physical signs in the chest are identical. One point of difference, however, is often apparent and that is in the response to atropine. An attack produced by mecholyl is promptly and completely controlled by atropine, whereas a spontaneous attack may be little influenced by atropine even in high doses. In a series of 22 cases of asthma treated by the high dose atropine method results were generally disappointing; the treatment failed to control the attacks completely in 50 per cent. of the cases. Dosage was usually raised to over 3 mg. daily. Melli and Molinari-Tosatti (1938) have used much higher doses, up to 13 to 20 mg. of atropine daily. In about two-thirds of their patients they failed to obtain complete freedom from attacks, although usually improvement was noted when the dose of 6 to 7 mg. daily was reached. This failure of atropine to control attacks of asthma requires an explanation, and may depend upon the different action of atropine in preventing the effects of injected acetylcholine, while not always preventing the effects of nerve stimulation at those sites where acetylcholine is believed to be the transmitter.

Dale and Gaddum (1930) have suggested that 'in such cases the nerve impulses liberate acetylcholine so close to the reactive structures that atropine cannot intervene, whereas it can prevent its access to them when it is artificially supplied from without'. The attack produced by mecholyl is probably



similar to, but not identical with, a spontaneous attack of asthma. The difference may lie in the allergic reaction which complicates the mechanism of a spontaneous attack and releases histamine or an 'H-substance'. As yet observations have not been carried out to ascertain whether the respiratory symptoms produced with mecholyl in asthmatic subjects are due to simple bronchospasm or also to oedema of the bronchial mucosa. In a case, however, of urticaria of nervous origin it has been possible to reproduce a typical attack of urticaria with an injection of mecholyl, and Grant, Pearson, and Comeau (1935), in a study of six similar cases of urticaria, were also able to obtain definite attacks with another choline ester (carbaminoyl-choline). Our case appears to be of particular interest and the report is given in full:

Female, aged 38 years. Married, two children. For the last twelve years the patient has had a most anxious time at home. Marriage proved unsatisfactory and she became separated from her husband soon after the birth of her second child. In addition to having the entire responsibility of bringing up her two children on the slenderest financial means, she has had to nurse her mother, crippled with rheumatoid arthritis. One brother and one sister died suddenly at the ages of 33 and 38 years respectively from a 'stroke'. Although she will not admit it, there is a fear at the back of her mind that she will die in a similar way. She does not think that she is unduly worried by the war, but her actions show that she is much more worried than she will admit. Since the outbreak of war the patient has developed on various occasions a severe urticarial rash over her whole body. In a mild form this rash appears practically every day, severe attacks occurring every week or fortnight according to circumstances. The rash appears to be brought on by emotional upsets, e.g. loss of temper or when visitors are calling on her, even when she has known the persons for many years. Exposure to heat and cold brings on a severe attack, but only when she has her head bent down, for example when clearing the hearth. Hot baths and drinking hot beverages have no effect at all. Exertion may also bring on an attack. The rash first appears on her face and spreads down her neck and shoulders, then over her chest and arms and finally over the legs. No rash ever appears on the palms of her hands, fingers, or the soles of her feet. The hands become dead white and bloodless and feel very cold, while her arms are very red and hot. The urticarial rash begins with flushing of the skin and then appears on the flushed area. In severe attacks it resembles giant urticaria. Itching usually accompanies the rash, which is most irritating and at times intolerable. Symptoms accompanying severe attacks are shivering, palpitation, noises in the head, a feeling of pressure on the head, and a scalding sensation from head to foot. After the attacks she usually has a bad headache and an unpleasant taste in the mouth. She feels very tired and falls asleep easily.

*Test with mecholyl.* A subcutaneous injection of 10 mg. of mecholyl was given into the right arm (zero time). At one and a half minutes salivation and lachrymation. At three and a half minutes flushing of the face and arms. At six minutes profuse sweating and a feeling of tightness of the chest. No rhonchi could be heard. At seven minutes an urticarial rash began to appear over the flushed area of the right arm. At twelve minutes the urticarial rash had become more marked and had spread to the whole of the right arm, left arm, chest, abdomen, and thighs. No rash was present on the palms of the hands or fingers, which were dead white and cold. No itching accompanied the rash. At twenty-nine minutes the urticarial eruption was at its height.



Atropine 1/100 gr. was injected subcutaneously and the urticaria began to fade four minutes later.

No attacks of urticaria have been observed in all the examples of true asthma or in the controls tested with mecholyl. Often a transient flare, but no definite wheal, was noted at the site of the injection. Flushing of the skin was very common, but the blush never spread to the palms of the hands or the fingers. A marked line of demarcation could often be seen at the level of the metacarpophalangeal joints between the salmon pink colour of the flushed skin and the dead white appearance of the bloodless and cold fingers. The palms of the hands also remained white. In some cases cyanosis of the finger tips was noted.

Asthma has been attributed to an imbalance of the autonomic system with predominance of the vagus nerve. Eppinger and Hess (1917) adduced as evidence of increased vagal tone in asthmatics such phenomena as a slow pulse, low blood-pressure, and increased sweating. Observations, however, on the manner in which asthmatic subjects respond to choline derivatives compared with control subjects go to show that the whole of the parasympathetic system is not hypersensitive to the drug; results vary considerably in different subjects, but the percentage of cases showing marked symptoms of parasympathetic stimulation (sweating, salivation, and lachrymation) is not greater among the asthmatic than among the non-asthmatic group. Thus of 27 cases of asthma tested with 10 mg. of mecholyl, 11 (or 40.7 per cent.) gave a marked reaction; in a group of 31 non-asthmatic subjects (including nine medical students, seven hospital patients suffering from non-respiratory diseases, 13 patients with chest diseases other than asthma, and two patients with hypertensive heart disease and cardiac asthma) 14 (or 45 per cent.) were strong reactors to mecholyl (see Tables III and IV). The fact, therefore, that asthmatics have the facility of developing chest symptoms after an injection of mecholyl does not appear to be due to increased sensitivity to the drug of the whole of the parasympathetic nervous system, but to a peculiar sensitivity of the bronchial territory. It is the bronchial nervous system which is abnormally sensitive and not the whole parasympathetic nerves, as Eppinger and Hess maintained in their theory of vagotonia.

This is also borne out by observations made on the action of mecholyl on the heart, as shown by the electrocardiogram, in a small group of asthmatic and normal subjects. Electrocardiographic records have been taken just before and at short intervals after a subcutaneous injection of 10 mg. of mecholyl. No appreciable change in the A.-V. conduction time was noted, but a striking change was inversion of the T wave, particularly in leads 2 and 3. On terminating the action of mecholyl with a subcutaneous injection of atropine or adrenaline, the T wave was observed to resume its upright position, thus suggesting that the inversion of the T wave was the effect of stimulation of cholinergic nerves. In five cases of asthma a sharp inversion of T<sub>2</sub> and T<sub>3</sub> was noted in two cases during an artificially produced attack

of asthma; T2 became upright and T3 diphasic shortly after the attack had been controlled with adrenaline. In a third case T2 became inverted and T3, from being flat, became inverted after an injection of mecholyl, while two other cases did not show any significant change (see Table V). These findings might suggest increased sensitivity of the heart to mecholyl, but similar changes have been observed in one normal subject, and by Page (1935) in four out of six hypertensive subjects tested with the same dose of mecholyl. Therefore, one is forced to conclude that the action of mecholyl on the heart is not peculiar to asthmatic subjects, and that the vagal tone of the heart does not differ materially in asthmatic and non-asthmatic subjects.

TABLE V

*Effect of Mecholyl (10 mg.) on the T wave as shown by the Electrocardiogram in a Group of Cases of Asthma and of Normal Subjects, and after Terminating the Effect of Mecholyl with an Injection of Adrenaline*

Case No.	Type of case.	Before mecholyl.			After mecholyl.			After adrenaline.		
		T1	T2	T3	T1	T2	T3	T1	T2	T3
1	Asthma	+	+	+	+	—	—	+	+	±
2	Asthma	+	+	+	0	—	—	0	+	±
3	Asthma	+	+	0	+	—	—			
4	Asthma	+	+	+	+	+	+	+	+	+
5	Asthma	+	+	+	+	+	+	+	+	+
6	Medical student	+	+	±	+	+	—			
7	Medical student	+	+	—	+	+	—			
8	Medical student	+	+	±	+	+	±			
9	Medical student	+	+	0	+	+	—			
10	Medical student	+	+	+	+	+	+			

+ = upright, — = inverted, ± = diphasic, 0 = flat.

It is not within the scope of this paper to discuss fully the reasons of the peculiar tropism of mecholyl for the bronchial territory of the parasympathetic system in asthma. Clinical observations and experimental work in animals go to show that the excitability of the vagus nerve may be influenced generally by foreign proteins and more locally by antecedent lung damage. Stoland, Sherwood, and Woodbury (1929) have observed increased excitability of the vagus nerve (chronaxie) by the previous injection of serum. Dodel (1932) found that the action of pilocarpine in guinea pigs is enhanced by producing a chemical bronchitis by means of a few whiffs of chlorine gas, and that the inhalation of chlorine concentrated the vagotropic action of pilocarpine on the respiratory system. Villaret, Vallery-Radot, Justin-Besançon, and Claude (1937), in experiments on dogs and rabbits, also found that the respiratory disturbances produced by mecholyl were more intense after the inhalation of chlorine. In man it is often observed that an antecedent respiratory infection, such as pneumonia, whooping cough, measles, or bronchitis, predisposes to or determines the onset of asthma. When bronchography is carried out as a routine procedure in the investigation of cases of asthma, it is surprising how frequently bronchiectasis is found to be associated with the disease. Bronchiectasis is often quite symptomless and

may be wholly unsuspected until a lipiodol investigation has been carried out. In this connexion it is interesting to note that Watson and Kibler (1937), on examining the sputum of bronchiectatic patients, found an abundance of eosinophils in a high percentage of their cases. Patients with bronchiectasis show variable degrees of sensitivity when tested with mecholyl; only those with an associated asthmatic syndrome develop marked respiratory symptoms, but occasionally cases of bronchiectasis with no asthma also respond to mecholyl with slight chest symptoms, thus revealing a latent tendency to asthma. One may therefore conclude that lung sepsis and lung damage are important factors in determining an irritable bronchial nervous system.

Many observers have postulated a specific bulbar centre in asthma which is hyperexcitable to various stimuli. While it is difficult to exclude the possibility that asthma may be caused by stimulation of such a parasympathetic centre, the effects which have been described of mecholyl on the bronchi of asthmatic subjects suggest that the abnormality lies at the periphery and involves the bronchial nerve endings or possibly the bronchial muscle itself. Current conceptions of the transmission by acetylcholine of nervous impulses from the nerve endings to the effector organs also support this view. Hurst has defined asthma as 'the reaction of an over-excitable bronchial centre to blood-borne irritation and to peripheral and psychical stimuli', but in view of the observations mentioned above is inclined to think that 'bronchial system', to include the bronchi themselves, should be substituted for 'bronchial centre'. In conclusion, I would suggest that an essential factor in asthma is an irritable bronchus produced by lung damage; in some cases the cause of lung damage may be traced to a definite respiratory infection while in other cases the cause may be obscure, as when a latent middle lobe bronchiectasis is found to be associated with asthma and is discovered by routine bronchography.

Given an irritable bronchus, it is conceivable how asthma may be provoked by certain allergic, reflex, and psychic stimuli, which usually have no effect on normal subjects.

#### *Summary*

1. Observations on the effect of parasympathetic-mimetic drugs have been made in a series of cases of asthma and of other chronic respiratory diseases. Acetyl- $\beta$ -methylcholine (mecholyl or mecholin, Merck) has been used owing to its tropism for the bronchial nervous system.
2. Twenty-eight cases of asthma have been investigated, and asthmatic subjects almost invariably responded with respiratory symptoms, which varied in intensity from slight wheeziness to a severe asthma-like attack.
3. Control subjects showed general signs of parasympathetic stimulation (flushing, sweating, lachrymation, and salivation), but did not develop chest symptoms.

4. The peculiar tropism of choline derivatives for the bronchial system appears to be due not to a state of increased sensitivity of the whole of the parasympathetic system (vagotonia), but only of the bronchial nerve endings or of the bronchial muscle itself.

5. Lung damage is an essential factor in determining the abnormal bronchial response.

6. The test with mecholyl does not help to differentiate the various types of asthma; it may, however, assist in the diagnosis between true bronchial asthma and respiratory neurosis (hysterical hyperpnoea). No matter how mild or infrequent the attacks of asthma may be, an asthmatic subject is nearly always susceptible to the drug.

7. The asthma-like attack produced by choline derivatives is similar to, but probably not identical with, spontaneous asthma.

I wish to express my thanks to the medical students who so readily volunteered to help with this study.

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# PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1940

## THIRTY-FOURTH ANNUAL GENERAL MEETING

THE THIRTY-FOURTH ANNUAL GENERAL MEETING was held in London at the Royal Society of Medicine on Friday, May 10, 1940. The attendance book was signed by 133 members. The proceedings began at 10 a.m.

*The President*, Professor J. G. Emanuel, was in the Chair.

*Death of Honorary Member.* The death of Professor G. R. Murray was recorded with regret, the President referring to the affection in which he was held and to his presidency of the Association at Manchester.

*The Minutes* of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

*The Treasurer* presented the Annual Accounts, which showed a balance of £286. 3s. 0d.

*Selection of Place of Meeting for 1941.* A letter had been received from Sir E. Farquhar Buzzard, on behalf of the Oxford members and the Staff of the Radcliffe Infirmary, inviting the Association to meet in Oxford in 1941. This invitation was unanimously accepted.

*Suspension of Rule 20.* It was agreed that Rule 20 be suspended for the duration of the present emergency.

### *Election of Officers*

*President.* Sir Robert Hutchison was elected President. On his election he took the Chair, and expressed the thanks of the Association to the retiring President, Professor J. G. Emanuel.

Election of Officers, Executive Committee, Honorary Member, Extra-Ordinary Members, and Ordinary Members then followed.

### *Executive Committee*

*President.* Sir Robert Hutchison.

*Treasurer.* Dr. H. Letheby Tidy.

*Secretary.* Professor L. J. Witts.

### *Members for England:*

Dr. A. E. Barnes.  
Dr. J. Murray Bligh.  
Dr. George Graham.  
Dr. C. E. Lakin.  
Professor L. G. Parsons.  
Professor O. L. V. S. de Wesselow.

### *Members for Scotland:*

Professor R. S. Aitken.  
Professor L. S. P. Davidson.  
Professor A. W. Harrington.



*Members for Ireland :*

Professor G. Bewley.  
Dr. R. H. Micks.  
Dr. J. A. Smyth.

*Honorary Member :*

Professor J. G. Emanuel (President 1939-40).

*Extra-Ordinary Members :*

Dr. H. Carlill.  
Sir Percival Horton-Smith Hartley.  
Professor F. Langmead.  
Dr. H. J. Starling.

*Ordinary Members :*

William Donald Wykeham Brooks, D.M., Physician to Out-patients, St. Mary's Hospital.  
Wilfred Fletcher Gaisford, M.D., Physician, Dudley Road Hospital, Birmingham.  
Thomas Newall Morgan, M.D., Assistant Physician, Aberdeen Royal Infirmary.  
Rupert Samuel Bruce Pearson, D.M., Assistant Physician, King's College Hospital.  
John Basil Rennie, M.D., Assistant Physician, Western Infirmary, Glasgow.  
Alan Filmer Rook, F.R.C.P., Consultant in Medicine, Royal Air Force.  
John Guyett Scadding, M.D., Assistant Physician, Brompton Hospital.  
Eric Frank Scowen, M.D., Assistant Director, Medical Professorial Unit, St. Bartholomew's Hospital.  
Lionel Ernest Howard Whitby, M.D., Clinical Pathologist, Middlesex Hospital.  
Paul Hamilton Wood, F.R.C.P., Assistant Physician, National Heart Hospital.

## SCIENTIFIC BUSINESS

*Friday Morning*

1. DR. R. E. SMITH discussed *The Use and Abuse of Paracentesis Tympani*. A study of the natural history of otitis media showed that the drum should not be opened if the patient's temperature were not above 100° F., or if the drum were only injected or even if uniformly red, nor if there were haemorrhagic blebs, such as were often present in influenza. Furthermore, he believed a bulge was insufficient evidence for immediate operation. Of 150 consecutive cases, 58 had a bulging drum but were not subjected to myringotomy. Of these, 30 had perforated spontaneously and 28 had settled down without perforation; three of the perforations were followed by mastoiditis, but all were cured by operation. He estimated that a surgeon whose motto was that 'early myringotomy saves the mastoid' would have opened at least 100 of the 150 cases under review. Most of these cases were seen before the introduction of chemotherapeutic drugs, which he thought would definitely abolish myringotomy, although it was dying a natural death before their invention.

DR. K. D. WILKINSON had seen severe cases recover without operation, but in others myringotomy had appeared to save life. DR. F. J. NATTRASS thought that the age factor was important and that Dr. Smith's results at a public school could not necessarily be applied to young children. In answer to questions by DRs. C. E. NEWMAN and GEOFFREY EVANS, DR. SMITH replied that pain rarely lasted longer than twenty-four hours, and was relieved by remedies such as aspirin; myringotomy appeared to increase the incidence of complications.

2. DR. E. P. SHARPEY-SCHAFER (introduced by PROFESSOR F. R. FRASER) spoke on *The Sex Hormones and Flushing*. The vasomotor symptoms that follow gonadal deficiency are stopped in both sexes by the androgens and the oestrogens. In normal females and normal males large doses of the androgenic substance, testosterone propionate, produce flushes, which can in turn be stopped by the simultaneous administration of the oestrogens. The oestrogens by themselves in large doses do not cause flushing in normal subjects of either sex. These results suggest that the sex hormones are not specific for a particular sex in regard to vasomotor symptoms, and that a simple deficiency of the male hormone in the male and the female hormone in the female is not an adequate explanation of vasomotor symptoms.



DR. PARKES WEBER, who surprised members by confessing ignorance of Turner's syndrome, suggested trying the effect of the sex hormones on troublesome flushing and sweating after eating.

3. DR. J. N. CUMINGS (introduced by DR. E. A. CARMICHAEL) described an investigation of the *Potassium Content of Muscle in Various Diseases*, in which it was shown that the potassium content was lower in myotonic but higher in myasthenic muscles than in normal muscle. The interruption of nerve impulses to normal muscle did not affect the potassium concentration. One action of prostigmin on muscle was to produce an approximation to the normal potassium concentration. Records of the results obtained in balance experiments demonstrated that there was no increased urinary output of potassium, although an increased quantity of potassium was present in the serum, which had been liberated from the affected muscles.

4. DR. B. MCARDLE (introduced by PROFESSOR J. A. RYLE) presented data from 40 cases on the *Serum-Potassium in Uraemia*. A flaccid paraplegia with absent reflexes and without sensory changes developed in a case of anuria with a serum-potassium of 41.6 mg. per 100 c.c., and in another case following the injection of 12 oz. of 3 per cent. potassium citrate per rectum. The paralysis was similar to that of Family Periodic Paralysis, which is, however, associated with a lowered serum-potassium. Gross asthenia was present in another patient with a serum-potassium of 26.7 mg. per 100 c.c., but whose serum-chlorides were 452 mg. per 100 c.c. It was suggested that the paralysis was due to potassium intoxication, though other cases with raised serum-potassium were observed without paralysis.

5. DR. W. A. R. THOMSON (introduced by PROFESSOR O. L. V. S. DE WESSELOW) discussed *The Significance of Potassium in Cardiovascular Disease*. After the administration of potassium salts by mouth, an increase in the height of the T wave occurred, and varying degrees of auriculoventricular and sino-auricular heart-block had been recorded. In view of the apparent close association between acetylcholine and the potassium ion, the effect of the subcutaneous administration of mecholyl (an acetylcholine derivative) upon the action of the heart and upon the serum-potassium had been investigated. So far as these investigations had gone, the results suggested that the changes in cardiac function produced by mecholyl were similar to those produced by potassium, and that they were accompanied by an increase in the serum potassium.

The PRESIDENT said that it was interesting to see potassium attracting attention after calcium had so long monopolized the stage. PROFESSOR A. A. F. PEEL wished to know whether potassium could produce ill effects in a healthy subject. DR. PARKES WEBER emphasized the danger of treating arteriosclerosis with large doses of potassium iodide. SIR WALTER LANGDON-BROWN pointed out that Langley had shown the connexion between potassium and vagus action. PROFESSOR R. A. PETERS thought that potassium had important actions within, as well as on the surface of, cells. DR. IZOD BENNETT thought that DR. MCARDLE's data were insufficient to allow the conclusion that the paralyses he had seen in uraemia were due to retention of potassium. DR. MCARDLE replied with spirit.

6. SIR ARTHUR HURST demonstrated a film of *War Neuroses* made between 1917 and 1919. It had been reprinted, as it was thought that it would be unfortunate if the many lessons learnt in the diagnosis and treatment of neuroses were forgotten and had to be slowly re-learned. For example, it was three years before it was widely recognized that so-called 'shell-shock' and 'disordered action of the heart' were preventable neuroses, and that the very common contractures following trivial wounds were not organic, but could be cured at a single sitting by explanation, persuasion, and re-education, instead of requiring many months of physiotherapy.

DR. GORDON HOLMES emphasized the importance of immediate diagnosis and treatment to prevent the development and extension of neuroses. PROFESSOR J. A. RYLE said that all that had been said was equally true of the visceral neuroses, especially D.A.H. DR. J. C. SPENCE emphasized the value and importance of good Battalion Medical Officers, and PROFESSOR L. S. P. DAVIDSON thought that the film should be shown to all final year medical students. DR. GEOFFREY EVANS said that bed exercises were very valuable to prevent development of neuroses in patients with organic disease.

7. COLONEL A. W. STOTT and MAJOR W. S. C. COPEMAN reported that, in addition to cerebrospinal fever, another form of meningococcal infection—*Chronic Meningococcal Septicaemia*—has made its appearance in the British Expeditionary Force, and about

30 cases have now been identified. Although a positive blood-culture is the only certain method of diagnosis, the isolation of the meningococcus from the blood presents difficulties, and repeated cultures are often necessary for success. The clinical picture, however, is so characteristic that bedside diagnosis should generally be simple.

The onset is usually sudden with fever, shivering, or actual rigor, severe headache, and severe migratory joint and muscle pains. Joint effusions are not uncommon. Within a few days a characteristic rash appears. Many lesions have been described and more than one type is usually present. The commonest are pink to red macules, papules, and nodules, from a few millimetres to 2 cm. or more in diameter. The papules and nodules sometimes have a small haemorrhagic centre and are usually tender. Petechiae are not uncommon. The rash is distributed over the limbs and back; fewer lesions occur on the face, chest, and abdomen; successive crops appear, each lasting a few days. A crop often appears with a rise of temperature. Brownish discoloration remains on fading. The fever is either regularly intermittent or of a more irregular type with afebrile periods, during which the patient may feel well and be discharged to duty, only to relapse in a few days. The spleen is sometimes palpable. These cases are commonly diagnosed as rheumatic fever, influenza, or erythema nodosum. Trench fever has been diagnosed in a few cases because subcutaneous nodules on the front of the legs have simulated 'tenderness of the shins'. The chief complications are meningitis and infective endocarditis. Nephritis and epididymitis also occur. Two cases of cerebrospinal fever have been seen with a history strongly suggesting that they had suffered from chronic meningococcal septicaemia for two to four weeks prior to the onset of meningitis.

Sulphapyridine in moderate doses by mouth rapidly terminates the disease and enables the patient to be discharged to a convalescent depot or to duty in a few days.

Such literature as they have been able to consult appears to deal with sporadic cases. They believe that chronic meningococcal septicaemia is probably a common condition whenever cerebrospinal fever becomes prevalent in a community.

Clinical observations were made by PROFESSORS A. W. M. ELLIS, J. A. RYLE, BRUCE PERRY, and J. W. MCNEE.

#### Luncheon

Luncheon was held at the Langham Hotel, and the President pointed out that the objects of the Association, which were the advancement of internal medicine and the promotion of friendship among physicians, were even more important in war than in peace.

#### 3 p.m. Afternoon Session

1. DR. PAUL WOOD discussed the difficulty in distinguishing *Pulmonary Embolism* from posterior myocardial infarction, both clinically and with limb lead electrocardiograms. The familiar Q3 T3 pattern may occur in both. Multiple chest lead electrocardiograms, however, show sharply dissimilar features: with posterior infarction there may be depression of the RS-T segment in lead IV, or there may be very tall T waves in any of the chest leads, or there may be no changes; with pulmonary embolism there is sharp inversion of the T wave, maximal and of longest duration in the right pectoral lead, minimal and of shortest duration in lead IV. These changes are transient, and from observations made on a variety of conditions appear to be due to right ventricular stress. They were found in nine out of ten cases of large pulmonary embolism.

2. DR. HUGH BARBER spoke on *Contusion of the Heart*. Case histories, suggesting the probability that the heart-muscle had been bruised, were recounted; and the following heart lesions, as the result of direct violence to the chest, were discussed—myocardial contusion, delayed rupture of the heart, haemopericardium, myocardial weakness, heart-block, angina of effort, valvular lesion, and auricular fibrillation.

DR. PAUL WOOD and PROFESSOR A. A. F. PEEL both thought that contusion of the heart was a dangerous diagnosis, and suggested alternatives such as trauma to a coronary vessel or pericarditis. SIR MAURICE CASSIDY and DR. G. C. DOCKERAY, on the other hand, described cases which appeared to support the diagnosis of contusion.

3. DR. A. F. FOSTER-CARTER (introduced by DR. C. HOYLE) discussed *Bronchial Adenoma*. Twenty-two examples of this condition seen at the Brompton Hospital were compared with 100 others taken from published records. The tumour was found to occur most often between the ages of thirty and forty years, the early clinical and radiological

features were often inconspicuous, and gross changes appeared only when a bronchus had become obstructed. It was shown that this growth had often been confused with bronchial carcinoma, but that it never produced metastases, and responded well to early treatment. Pulmonary infection was the most frequent and serious complication.

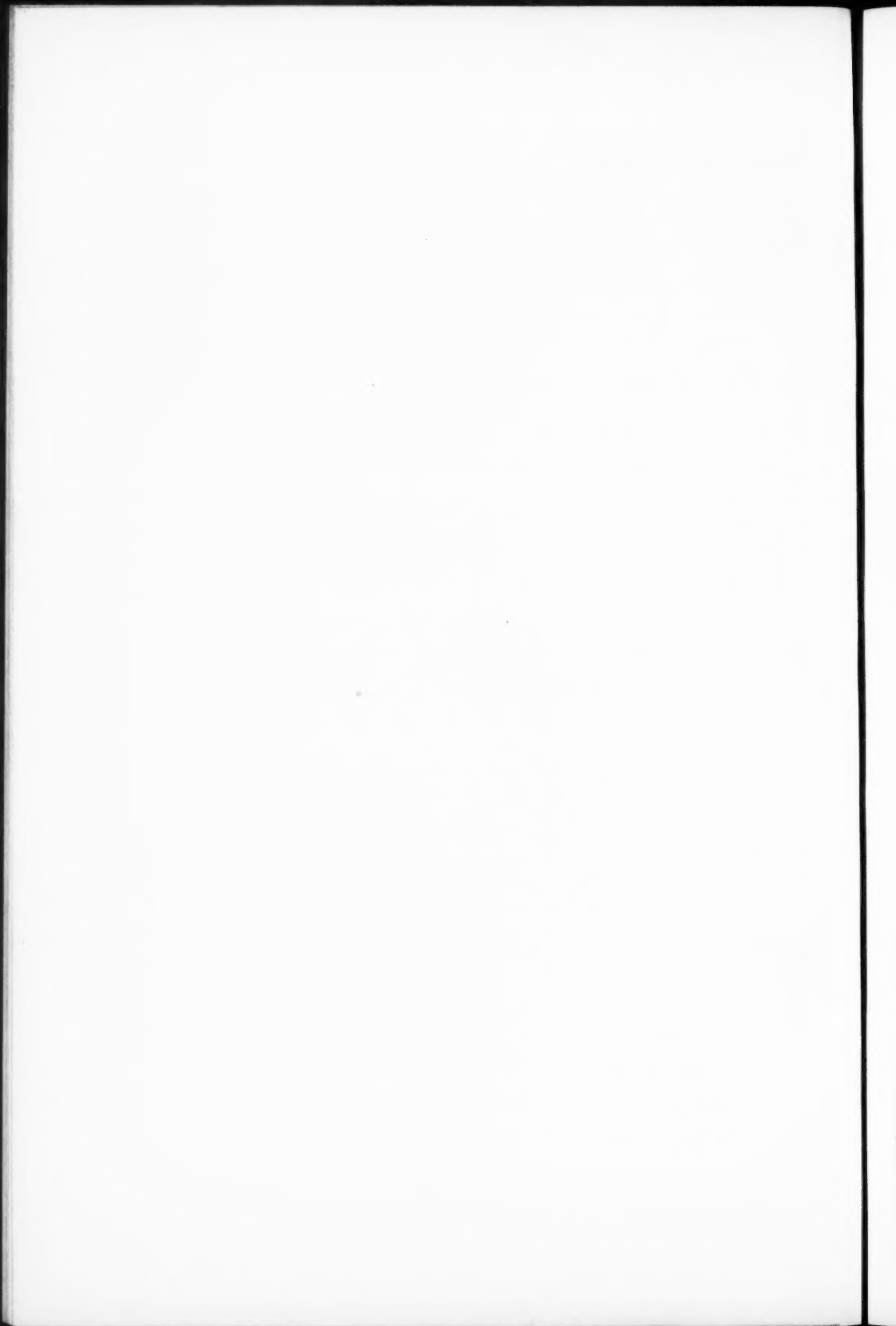
DR. F. G. CHANDLER thought it was important that the pathological classification of these tumours should be revised and simplified. Drs. J. L. LIVINGSTONE, W. D. W. BROOKS, CLIFFORD HOYLE, and PAUL WOOD each described cases with noteworthy features. SIR ARTHUR HURST compared the relative sex incidence of adenoma and carcinoma of the bronchus and the large bowel, and pointed out that the greater frequency of adenoma in the female was correlated with the higher incidence of malignant disease of the sex organs in the female.

4. DR. T. IZOD BENNETT, discussing the *Varieties and Pathogeny of Idiopathic Steatorrhoea*, said that confusion occurred through Continental writers not having much experience either of coeliac disease or of tropical sprue, two clear-cut diseases well known to British physicians. Amongst supposed cases of idiopathic steatorrhoea were many which were examples of coeliac disease discovered during, or surviving into, adult life; a certain number of other cases were cases of tropical sprue developing many years after the patient had returned to the Western world. But a few cases were occasionally met with in which the syndrome appeared in adult life without explanation. The condition is in every case the result of jejuno-ileal insufficiency. The final proof of this is found in the production of the complete syndrome following anastomosis between the jejunum and the colon.

5. DR. MANSON-BAHR exhibited paintings of the *Tongue Changes in Sprue, Pellagra, Pernicious Anaemia, and Idiopathic Steatorrhoea*. The object of his communication was to show that, on the whole, the glossitic changes in these several diseases were so similar that they might be considered identical. Even angular stomatitis (cheilosis) was not a specific feature. The glossitis of these diseases is therefore non-specific, but constitutes a link between these clinically dissimilar states and may represent a Vitamin B<sub>12</sub> deficiency.

PROFESSOR J. A. RYLE thought that there was always an organic lesion present in steatorrhoea, though it was often in the lacteal system rather than the small intestine. The word glossitis included two distinct entities, atrophy and inflammation or soreness. DR. HAMILTON FAIRLEY was not convinced that nicotinic acid had any effect on sprue, pointing out that DR. MANSON-BAHR had given liver as well. PROFESSOR L. S. P. DAVIDSON said that in many of these syndromes, e.g. iron deficiency, there was a vicious circle. Deficiency gave rise to alimentary failure, and that in turn conditioned further deficiency.

Although the minds of many were pre-occupied by the sudden extension of hostilities on the morning of May 10, there was agreement on the wisdom and success of meeting in time of war. However short a meeting, many members seem unable to see it through to a finish. This is more often due to intellectual sloth than to urgent need for their services elsewhere, and it is discourteous to the speakers whose names appear in the later part of the programme.



## A HAEMORRHAGIC DIATHESIS IN IDIOPATHIC STEATORRHOEA: OBSERVATIONS ON ITS ASSOCIATION WITH VITAMIN K DEFICIENCY<sup>1</sup>

By ROBERT KARK, ALEXANDER W. SOUTER  
AND JOSEPH C. HAYWARD

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston; and the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.)

A HAEMORRHAGIC state is seldom encountered in sprue, coeliac disease, and idiopathic steatorrhoea (non-tropical sprue), and in a study of over 200 cases of sprue in Puerto Rico, Castle (1940) did not observe any haemorrhagic manifestations. Hess and Saphir (1935), who reviewed the literature of coeliac disease, made no mention of such a complication, nor did Thaysen (1932) in his monograph on idiopathic steatorrhoea. Observations are recorded below on a patient with idiopathic steatorrhoea who developed an associated haemorrhagic diathesis distinct from scurvy, together with a collection of similar cases from the literature (Table I). An account is given of experimental studies on the action of vitamin K analogues in the haemorrhagic condition which occurred in our patient.

### *Case Report*

A man with idiopathic steatorrhoea, after 2½ years' treatment with a low-fat diet, develops a severe haemorrhagic tendency with marked hypoprotrombinaemia which is corrected by oral administration of 'synthetic vitamin K'.

J. M., a 62-year old, white, married man, a barber by trade, was admitted to the Evans Memorial Hospital, Boston, Massachusetts, on 20th November 1939, complaining chiefly of generalized bruising and weakness. He was a native of Massachusetts and had not been out of New England. In 1919 he had an attack of diarrhoea, which lasted three weeks and was believed to be due to contaminated well-water, since many others were similarly affected at this time.

In 1936, some three years before admission, he began to suffer from gradually increasing weakness which was attributed by his own doctor to anaemia. Therapy with iron was commenced. Shortly afterwards he developed severe diarrhoea, passing as many as 10 to 15 watery stools daily, and having concomitant anorexia and attacks of vomiting. He was given intramuscular injections of liver extract, with subsequent decrease in the number of stools and cessation of vomiting.

<sup>1</sup> Received June 7, 1940.

Authors	Number of cases	Clinical diagnosis	Haemorrhagic manifestations	Clotting time	Bleeding time	Capillary fragility	Platelets	Duration of illness prior to low-fat diet	Duration of low-fat diet prior to haemorrhages	Gums	Perifollicular haemorrhages	Therapy	Results and Remarks
Still (1918)	5	Coeliac disease	Scurvy	..	..	..	..	..	..	..	..	..	..
	2	Coeliac disease	'Purpura'										
Winter (1926)	1	Coeliac disease	Haemarthroses; ecchymoses on legs and arms	+	..	Negative	..	..	..	..	..	Intra-articular blood	Improved
Fanconi (1927)	3	Coeliac disease	'Haemorrhagic diathesis clinically unlike scurvy and resembling haemophilia'	+	+	Negative (one case)	Normal	..	..	..	..	..	..
Holst (1927)	1	Non-tropical sprue	<i>Post mortem</i> : Severe haemorrhages in jejunum without intestinal lesions; blood in pericardium; sub-dural blood; haemorrhage in heart muscle	..	..	..	100,000	..	..	..	..	..	Death from sudden haemorrhage
Lehndorff and Mautner (1927)	None	Review of coeliac disease	<i>Late cases</i> : Haematomata; large ecchymoses; purpura with mucosal haemorrhage	..	..	..	..	..	..	..	..	..	? Due to 'Angiomalacia'
Smith (1927)	1	Coeliac disease	Subcutaneous haemorrhages on knees, elbows, and back; blood in urine and stools	..	..	..	..	13 months	5 months	Normal	..	Intra-peritoneal blood	Some improvement
Fanconi (1928 and 1936)	5	Coeliac disease	'Scurbutoid' condition	+	Normal	Negative	Normal or raised	..	..	..	..	..	..
Strandquist (1929)	1	Coeliac disease	Epistaxis; subcutaneous haemorrhages; and ecchymoses on forehead, arms, and legs. <i>Later</i> : Death with epistaxis and haematemesis	+	+	+	210,000	18 months	12 months	Normal	..	Transfusion	Unimproved
Feistley (1930)	1	Sprue	Epistaxis	Normal	..	..	..	..	..	..	..	Diet including liver	Improved
Bloch (1930)	1	Coeliac disease	Haematoma on eyelid (cured with lemon juice), and haematuria. <i>Later</i> : Generalized subcutaneous ecchymoses with bruises at venepuncture sites	..	..	..	..	..	..	..	..	..	Coincident vitamin A deficiency from low-fat diet
Thaysen (1935)	1	Idiopathic steatorrhea	Ecchymoses on legs	..	..	..	Normal	Since infancy	..	Normal	..	Liver	..
Fullerton and James (1936)	1	Idiopathic steatorrhea	Haematemesis; epistaxis; ecchymoses on legs and arms; purpura on thigh, trunk, and legs	+	+	..	Normal	Since infancy	24 months	Normal	Normal	Concentrated liver extract and transfusion	Improved Later transfusion admitted and died
Fanconi (1938)	1	Coeliac disease	Scurvy cured, then 'hypothrombinaemia' (clinical manifestations not given)	+	Normal	Negative	161,000	..	..	..	..	Transfusion and liver	..
Bassett <i>et al.</i> (1938)	1	Idiopathic steatorrhea	Haematemesis; ecchymoses of legs; blood in urine and stools; haematoma of groin	+	+	Negative	Normal	..	24 months	Normal	..	Transfusion and ascorbic acid	Slow improvement and recurrence



His diet, which up till that time had been low in fresh fruits and vegetables, adequate in meat, milk, eggs, and cheese, and high in butter and fried and fatty foods, was altered on the advice of his physician to include orange juice and more fresh fruits and vegetables, while fried and fatty foods were restricted. From that time he constantly experienced some general malaise, weakness, diarrhoea, and difficulty in walking, which he attributed to stiffness of the legs. The stools were generally pale or white in colour, but not bulky or foul, and they varied from 4 to 5 daily. Injections of concentrated liver extract were continued once every two or three weeks, supplemented during the last two years by the daily ingestion of one-half pound of raw liver. Moderate oedema of the ankles occasionally appeared at the end of his day's work, and transient purpuric spots had been noted on his extremities at times during the eighteen months prior to admission. A gradual loss of weight from 156 lb. to 130 lb. was also a feature of his illness. At no time did he experience soreness of the tongue or bleeding from the gums.

An acute exacerbation of symptoms with severe diarrhoea, vomiting, and marked oedema of the ankles occurred in July, 1939. He entered a hospital, where a diagnosis of 'colitis' was made. During his stay in that hospital his symptoms abated somewhat and he was later able to continue with his work, although moderate diarrhoea and weakness persisted. Three days before admission to the Evans Memorial Hospital he suddenly became extremely weak and felt faint. Tingling and numbness of the hands and feet appeared. Many large ecchymoses were noted especially about the wrists, left elbow, and right knee. The hands and wrists became swollen and discoloured, and oedema of the feet and ankles rapidly increased. He also observed that his urine was dark in colour, and that the stools were black. A trivial skin injury over the right wrist sustained two days before admission gave rise to a slow oozing haemorrhage which persisted in spite of treatment by bandaging, the blood soaking through a succession of bandages.

On admission he was found to be very emaciated. The skin was pale and brownish-yellow in colour, but not icteric. Large ecchymoses were present over the backs of the hands and wrists, and about the left elbow, right knee, and the right side of the back over the scapular area (Fig. 1). A bandage round the right wrist was soaked with blood. No perifollicular haemorrhages were seen. Some bronzing of the skin was present about the hands, forearms, and lower part of the legs. The conjunctivae were pale and there was some lachrymation and photophobia. A fine fluttering tremor of both lower eyelids was observed. No ulceration or fissures were seen on the lips or in the mouth; the gums were neither discoloured nor spongy, and no bleeding was observed. The tongue was pale, the papillae being slightly coated, but not atrophic. The pulse rate was 96 per minute and the blood-pressure 80/50 mm. of mercury. The heart was not enlarged clinically and, apart from a widespread soft systolic murmur, no abnormal sounds were heard. The abdomen was tympanitic, but otherwise normal. Rectal examination was negative. Both wrists were swollen and tender and showed limitation of movement. Carpal spasm was present and Trousseau's and Chvostek's signs were positive. All tendon reflexes were absent. The plantar responses were flexor. Vibratory sensation was diminished in the legs. There was marked oedema of both legs, extending up to the thighs. No retinal haemorrhages were observed.

*Laboratory Data.* Urine: albumin 0.05 per cent.; the sediment contained

many red blood-cells and a few white blood-cells. Faeces: watery, dark brown in colour, with excess mucus; guaiacum test positive. Blood: haemoglobin 5.3 gm. per 100. c.c.; red blood-cells 2,090,000 per c.mm.; white blood-cells 7,300 per c.mm. with a differential count of polymorphonuclear neutrophils 83 per cent., lymphocytes 9.5 per cent., and monocytes 7.5 per cent. Haematocrit 19 per cent. Cells: mean corpuscular volume  $96.4 \mu^3$ ;

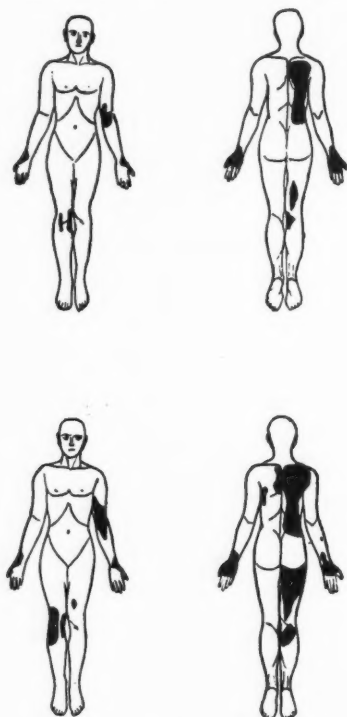


FIG. 1. The extent of subcutaneous haemorrhages in the patient on his admission (upper figures), and 24 hours later (lower figures).

mean corpuscular haemoglobin  $25.3 \gamma\gamma$ ; mean corpuscular haemoglobin concentration 26.3 per cent. The fragility of the red blood-cells to hypotonic salt solutions was normal. Blood Chemistry: serum-calcium 5.0 mg., and serum-phosphorus 1.6 mg. per 100 c.c.; serum-phosphatase, 16 units (King-Armstrong); total plasma-proteins 3.78 gm. per 100 c.c., albumin 1.93 gm. per 100 c.c., globulin 1.59 gm. per 100 c.c.; and non-protein nitrogen 26.4 mg. per 100 c.c. Blood: Hinton and Kahn tests negative. Test Meal: 25 units of free hydrochloric acid after histamine injection. Sugar Tolerance Test: (50 gm. of dextrose orally) showed a flat curve. Stool Fat: following the intake of 100 gm. of fat; 62.5 gm. of fat were excreted, of which 21.4 gm. consisted of neutral fat and 41.1 gm. of fatty acids.

A diagnosis of idiopathic steatorrhoea complicated by tetany and a haemorrhagic diathesis was made. The patient was treated with rest in bed, a low-fat diet, calcium gluconate administered orally and intravenously, vitamin D, and ferrous sulphate. During his first day in the hospital the

bleeding of the right wrist was controlled by pressure bandages and ice bags. At this time he apparently had a haemorrhage into the right knee-joint which became extremely painful, swollen and tender, and showed marked limitation of movement.

*Investigation of the Haemorrhagic Diathesis*

*Methods.* The coagulation time of venous blood was determined by the method of Lee and White as modified by Pohle and Taylor (1937). Estima-

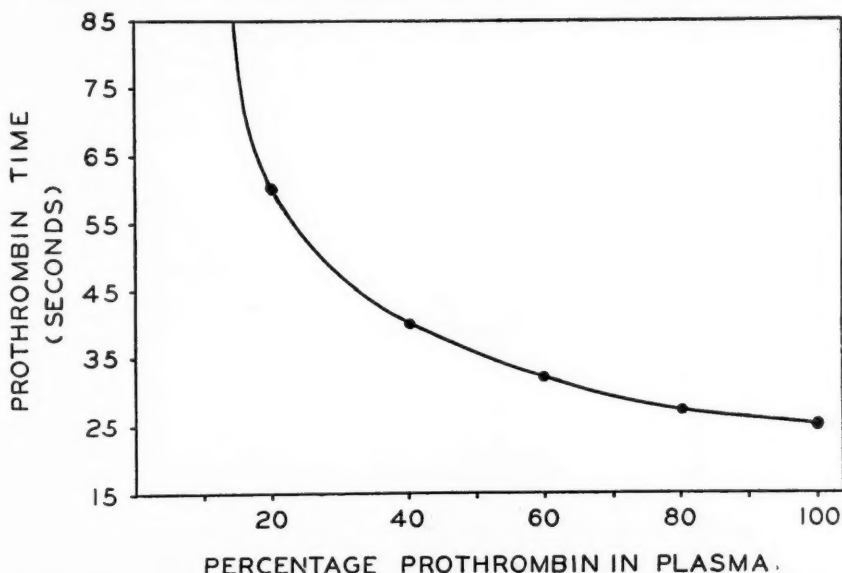


FIG. 2. The relation between the prothrombin percentage of human plasma and the Quick prothrombin time in the presence of excess tissue thromboplastin.

tion of the bleeding time was made by the Duke method. The blood prothrombin time was determined by the method of Quick (1935). This test measures the time taken for a sample of plasma to coagulate after recalcification in the presence of an excess of tissue thromboplastin. A comparison is made with normal plasma treated in a similar manner. Conversion of these 'times' to blood prothrombin percentages was made by reference to a curve constructed according to the method of Kark and Lozner (1939). By this method varying dilutions of normal plasma with prothrombin-free plasma are set up and the Quick prothrombin time is determined on the mixtures which contain known percentages of prothrombin; from these figures a curve (Fig. 2) can be constructed allowing of conversion of prothrombin times to blood-plasma prothrombin concentrations. During this investigation the Quick prothrombin time of the normal control plasma varied between 19 and 25 sec., when different batches of thromboplastin

were used. For the sake of uniformity in the construction of charts the prothrombin times obtained were calculated on a basis of 25 sec. for the normal control (100 per cent. prothrombin).

*Hypoprothrombinaemia and vitamin K therapy.* After the patient had been in the hospital 24 hours there was an extension of all the haemorrhagic areas (Fig. 1). At this time the blood coagulation time was prolonged to

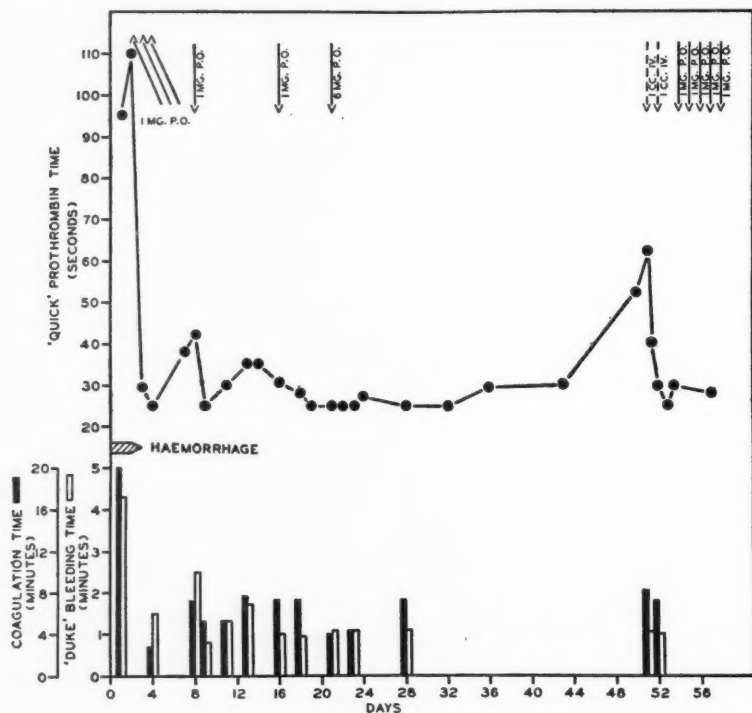


FIG. 3. The effect of 'synthetic vitamin K' (2-methyl-1, 4-naphthoquinone and a water-soluble derivative) on the Quick prothrombin time, blood coagulation time, and bleeding time of the patient with idiopathic steatorrhea.

20 min., the bleeding time was 5 min., with an excessive flow from the stab wound, and the capillary fragility was normal. The blood-prothrombin concentration was approximately 15 per cent. (Quick prothrombin time of 96 sec. against a normal control of 25 sec.) (Fig. 3). The blood-fibrinogen was 263.3 mg. per 100 c.c. The reduced ascorbic acid in the plasma was 0.2 mg. per 100 c.c. and the blood-platelet count showed 170,000 per c.mm.

The next day there was continued melaena and haematuria, and the pain and swelling of the right knee-joint was more severe. The blood-prothrombin concentration had fallen below the level of the previous day (Quick prothrombin time of 110 sec.). A diagnosis of haemorrhagic diathesis consequent on severe hypoprothrombinaemia was made and he was given

1 mg. of 2-methyl-1, 4-naphthoquinone ('synthetic vitamin K')<sup>2</sup> by mouth. Twenty-four hours later the blood-prothrombin concentration was 70 per cent. (Quick prothrombin time of 29 sec.). That day he was given a further 2 mg. of 2-methyl-1, 4-naphthoquinone orally and in twenty-four hours the blood-prothrombin time was normal, the blood coagulation time  $3\frac{1}{2}$  min. and the bleeding time  $1\frac{1}{2}$  min. From this time on there was no further extension

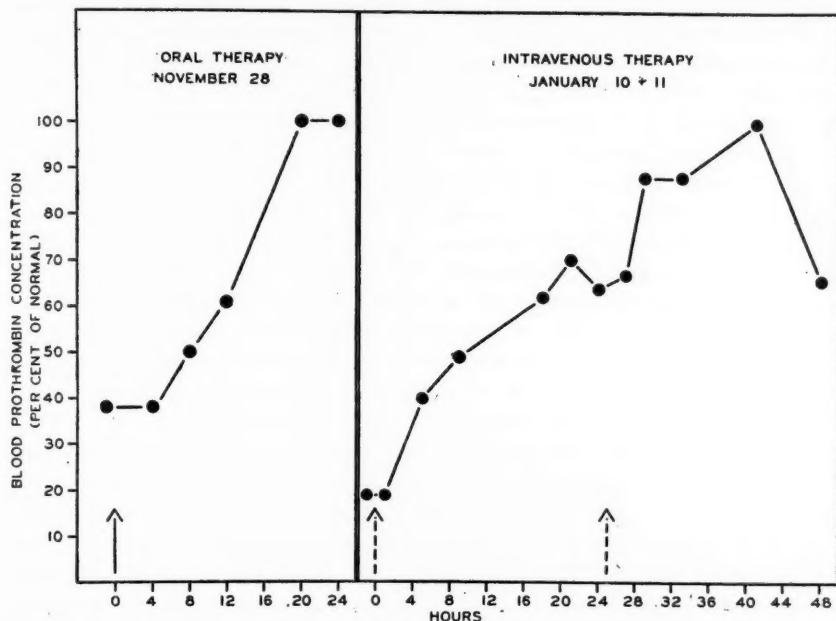


FIG. 4. The effect on the blood-prothrombin concentration of the patient with idiopathic steatorrhoea of 1 mg. of 2-methyl-1, 4-naphthoquinone by mouth (solid arrow) and the effect of 1 cc. of a solution of a water-soluble derivative of 2-methyl-1, 4-naphthoquinone (equal in vitamin K activity to 1 mg. of 2-methyl-1, 4-naphthoquinone by chick assay) administered intravenously on two occasions (broken arrows).

of the haemorrhagic areas. The haematuria dramatically cleared. Gross blood disappeared from the stools, but a positive benzidine test persisted for some days. The blood-prothrombin level, however, was not maintained and four days later it had dropped to 38 per cent. (Quick prothrombin time 42 sec.). The blood coagulation time was  $7\frac{1}{2}$  min. and bleeding time  $2\frac{1}{2}$  min. At that time he was given 1 mg. of 2-methyl-1, 4-naphthoquinone orally and his blood-prothrombin concentration was followed at four-hourly intervals thereafter (Fig. 4). In twenty-four hours the blood-prothrombin concentration had reached 100 per cent.

On 1st December, his twelfth day in hospital, he accidentally cut his wrist. Haemorrhage was slight and readily controlled. During the ensuing week his blood-prothrombin concentration fell somewhat, but on further

<sup>2</sup> We wish to thank E. R. Squibb & Son for supplying this compound.

treatment with 'synthetic vitamin K' it promptly became normal. About this time clinical improvement became evident following the cessation of the diarrhoea, and by 16th December, his twenty-seventh day in hospital, the ecchymoses had entirely disappeared and free movement of his right knee was re-established. During the next three weeks he maintained a high blood-prothrombin level.

A recrudescence of symptoms with tympanites, abdominal cramps, and diarrhoea occurred on 8th January, 1940. His blood-prothrombin content dropped rapidly during this relapse, and on 10th January when the abdominal symptoms were most marked the blood-prothrombin concentration had fallen to 18 per cent. (Quick prothrombin time 63 sec.). He was then given an intravenous injection of 1 c.c. of an isotonic solution of a water-soluble derivative of 2-methyl-1, 4-naphthoquinone equivalent in potency by chick assay to 1 mg. of 2-methyl-1, 4-naphthoquinone. One hour after the injection the blood-prothrombin concentration was unchanged (Fig. 4). Thereafter, the Quick prothrombin times were determined at four-hourly intervals. The maximum effect was observed twenty-one hours after injection when the blood-prothrombin level was 70 per cent. (Quick prothrombin time 29 sec.). Three hours later the blood-prothrombin concentration had fallen to 64 per cent. (Quick prothrombin time 32 sec.). The patient was, therefore, given a second injection of 1 c.c. of the solution intravenously and the blood-prothrombin concentration reached 100 per cent. eighteen hours later. During the next month, while his clinical condition steadily improved, the blood-prothrombin was maintained at a level of between 80 and 100 per cent. on a dosage of 1 mg. of 2-methyl-1, 4-naphthoquinone orally per diem.

*In vitro investigations with 2-methyl-1, 4-naphthoquinone ('synthetic vitamin K') added to human plasma.* As yet there is no knowledge of the chemical composition of prothrombin, nor of the processes involved in its manufacture within the body. For this reason we thought that it would be of interest to determine whether the addition of 2-methyl-1, 4-naphthoquinone to citrated plasma would affect the prothrombin concentration under various conditions. Five groups of experiments were carried out in duplicate and with adequate controls. From these experiments it was evident that the simple addition of various concentrations of 2-methyl-1, 4-naphthoquinone to plasmas containing reduced quantities of prothrombin was not effective in raising the prothrombin concentration *in vitro*. These plasmas were obtained from patients suffering from hypoprothrombinaemia, or were prepared artificially, using the method of Lozner, Kark, and Taylor (1939). Similarly, the addition of 2-methyl-1, 4-naphthoquinone failed to check the disintegration of prothrombin which occurred with incubation at 37.8° C. On the basis of these *in vitro* studies it seems reasonable to postulate that the effect of naphthoquinone in raising the blood-prothrombin concentration in patients with hypoprothrombinaemia is not the result of a simple chemical reaction with any constituent of plasma, neither does its effect appear to be 'protective' in retarding disintegration of prothrombin.



*Discussion*

*The haemorrhagic diatheses of idiopathic steatorrhoea.* The early clinical descriptions of the idiopathic steatorrhoeas by Gee (1888), Herter (1908), and Heubner (1909) do not include any mention of a haemorrhagic tendency in association with these conditions. Still (1918), in a survey of 41 cases of coeliac disease, recognized the occurrence of both scurvy and 'purpura' among his patients. 'Purpura' was observed as part of the terminal picture in some instances, and in one case it occurred while the patient was in a phase of remission as a result of treatment, probably with a low-fat diet. Fanconi (1927) published a report on three cases of coeliac disease associated with a haemorrhagic diathesis which he described and differentiated from scurvy, likening it to haemophilia because of a prolonged coagulation time in the presence of normal capillary fragility and blood-platelet counts. Such a haemorrhagic tendency he termed 'skorbutoid'. At this time Lehndorff and Mautner (1927), in their review of coeliac disease, divided cases showing a haemorrhagic tendency into two groups, typical scurvy, appearing early in the disease, and 'atypical scurvy', which was seen in the latter part of the illness and was characterized by the appearance of large ecchymoses and haematomata and occasionally haemorrhage from the mucous membranes. They attributed this atypical scurvy to 'angiomalacia' consequent on impaired nutrition of the walls of the small blood-vessels. Fanconi (1928, 1930) enlarged upon his previous concept of the 'skorbutoid' state and established that the haemorrhagic diathesis which in certain instances resembled fatal fulminating purpura was associated with a deficiency in the 'Gerinnungs-Ferment' (coagulation enzyme). He therefore termed the condition 'hypothrombinaemia'. Fullerton and Innes (1936) who described a case of idiopathic steatorrhoea in an adult, complicated by a haemorrhagic diathesis, suggested that the basis of the haemorrhage was some as yet unknown defect or deficiency, as they felt that the condition could not be accounted for by scurvy or even scurvy with an associated hypocalcaemia. Fanconi (1938) and Engel (1939) suggested that the 'skorbutoid' type of haemorrhagic diathesis associated with coeliac disease and sprue might be caused by a deficiency of vitamin K, and Butt, Snell, and Osterberg (1939) found a reduced blood-prothrombin concentration in two patients with non-tropical sprue, but in neither of these were there any haemorrhagic manifestations.

*Nutritional deficiency of vitamin K.* Dam (1935) described a deficiency disease of chicks which was cured by the addition of a fat-soluble material to the deficient diet. This disease was characterized by a haemorrhagic tendency of a 'haemophilic' nature and was shown by Dam, Schønheyder, and Tage-Hansen (1936) to be associated with a hypoprothrombinaemia. This returned to normal, with remission of the haemorrhagic state, when the fat-soluble material which he termed vitamin K ('Koagulations Vitamin') was administered to the chicks. Quick, Stanley-Brown, and Bancroft (1935)

showed that the haemorrhagic manifestations of obstructive jaundice were associated with a hypoprothrombinaemia and Warner, Brinkhous, and Smith (1938) and Butt, Snell, and Osterberg (1938) showed that the haemorrhagic manifestations and the underlying hypoprothrombinaemia of jaundiced patients could be cured by the oral administration of vitamin K concentrates together with bile salts. Shortly thereafter, Quick (1938) suggested that the critical level for haemorrhage in these patients was a blood-prothrombin concentration of approximately 20 per cent. of normal. Kark and Lozner (1939) described four cases of dietary deficiency exhibiting a hypoprothrombinaemia which was restored to normal by the administration of vitamin K concentrates alone, while the patients continued to partake of a deficient diet. Thayer, Brinkley, MacCorquodale, Doisy, Emmett, Brown, and Bird (1939) by degradation and synthesis showed vitamin K<sub>1</sub> to be 2-methyl-3-phytyl-1, 4-naphthoquinone. It is now established (Almquist and Klose, 1939) that many of the naphthoquinone derivatives exhibit vitamin K activity and that of these the compound 2-methyl-1, 4-naphthoquinone is the most active known and is three times as potent as the natural vitamin K<sub>1</sub>.

*Haemorrhagic hypoprothrombinaemia in idiopathic steatorrhoea.* Our patient presented a severe haemorrhagic diathesis which approximated in its clinical manifestations to that seen in obstructive jaundice and the 'skorbutoid' condition described by Fanconi. These manifestations were associated with a marked diminution in the blood-prothrombin concentration well below the critical level for bleeding, and the dramatic restoration of the blood-prothrombin level after the oral administration of 1 mg. of 2-methyl-1, 4-naphthoquinone ('synthetic vitamin K') alone, coincided with arrest of the haemorrhagic manifestations and return of the clotting and bleeding times to normal. Because of this we feel that these haemorrhagic manifestations were the result of a deficiency of the fat-soluble vitamin K.

It seems probable that this deficiency arises as a result of a combination of factors, insufficient intake, impaired absorption, and increased loss by excretion of vitamin K. The first is probably the most important single cause in those patients in whom the fat intake has been restricted almost completely over a prolonged period, as in the case we report. Study of the cases which we have collected from the literature exhibiting a haemorrhagic state distinct from scurvy (see Table, page 248) reveals that in all those whose dietary history is recorded, therapeutic restriction of fat intake had been carried out for a considerable time before the onset of haemorrhagic manifestations. Impairment of absorption, however, probably plays a part, in spite of the apparently contradictory evidence presented here in our patient's rapid response to the simple oral administration of minimal doses of 2-methyl-1, 4-naphthoquinone ('synthetic vitamin K'); natural vitamin K is an oily substance almost insoluble in water, while this synthetic compound is a crystalline material moderately soluble in water and saline, and therefore their absorption by the intestine in steatorrhoea may well differ somewhat.

The third factor, that of increased loss by excretion, is one common to all vitamins when prolonged diarrhoea occurs. We consider that, while a mild vitamin K deficiency can arise in patients with steatorrhoea taking mixed diets, the severe haemorrhagic manifestations of marked hypoprothrombinaemia do not occur until after the patients have taken for a long time a diet almost free of fat.

*The clinical picture of the haemorrhagic diatheses of idiopathic steatorrhoea.* There is no doubt that scurvy may be associated with the steatorrhoeas. It is generally seen in the early stages of the disease, and Still (1918) suggested that in children infantile scurvy might actually usher in the condition of coeliac disease. The 'skorbutoid' picture appears as a distinct entity, generally in the late stages of the steatorrhoeas and largely as a result of the regime prescribed for such patients, in which the fat intake and with it vitamin K, is radically reduced. It may be associated, as Bloch (1930) has shown, with the manifestations of deficiency of the fat-soluble vitamin A. It is wise, of course, to supplement the diets of patients with steatorrhoea with concentrates of the various vitamins and minerals, and among these vitamin K or one of its analogues should be included. In our patient we were able to maintain a normal blood-prothrombin concentration by the daily administration of 1 mg. of 2-methyl-1, 4-naphthoquinone orally while he was partaking of a low-fat diet.

When hypoprothrombinaemia is sufficiently marked, it may manifest itself by the spontaneous appearance of large subcutaneous haematomata, usually on the back, or on other sites of pressure. Dramatically, haemarthrosis, severe haematemesis, epistaxis, haematuria or melaena may be the presenting symptom. Menorrhagia has been noted. Intractable haemorrhage may occur from skin wounds, and we have noticed the constant appearance of haematomata at the site of venepuncture. Bleeding may occur from the gums after slight trauma, but the gums themselves do not show the purple sponginess characteristic of scurvy. Perifollicular haemorrhages are not a feature. The blood coagulation time is prolonged, but not to the same extent as it may be in haemophilia. The bleeding time is usually normal. The capillary fragility is unaltered as is the blood-platelet count. Marked prolongation of the Quick prothrombin time is present and is the crucial diagnostic finding. The condition differs markedly from scurvy which is more commonly seen in the early stage of the illness when the patient presents himself for diagnosis. This latter haemorrhagic condition is rarely seen in the patient who is having treatment, as it has long been recognized as a possible complication of steatorrhoea, and appropriate measures for its prevention are usually undertaken.

*Oral and parenteral administration of naphthoquinone derivatives.* During the patient's stay in the hospital we were able to compare the therapeutic effect of oral and parenteral administration of naphthoquinone derivatives. The parenteral material used was a water-soluble derivative of 2-methyl-1, 4-naphthoquinone synthesized by Moore and Kirchmeyer (1940) and

described previously (Kark and Souter, 1940). One c.c. of an isotonic solution containing this material was the equivalent of 1 mg. of 2-methyl-1, 4-naphthoquinone by chick assay.<sup>3</sup> The administration of the two naphthoquinone derivatives in this comparative study was carried out at times when the blood-prothrombin concentration had fallen to low levels, the patient's general condition on these two occasions being very similar. It will be seen from Fig. 2 that the oral administration of 1 mg. of 2-methyl-1, 4-naphthoquinone was without effect on the blood-prothrombin concentration during the first four hours after administration. Twelve hours after the drug had been taken the prothrombin level had risen by 20 per cent.; a normal level was attained ten hours later, and was maintained for at least a further four hours.

In contrast to this, the intravenous administration of an equivalent dose of the water-soluble derivative of naphthoquinone mentioned above produced a 20 per cent. rise of blood-prothrombin concentration within five hours, but a normal level was never reached, and by twenty-four hours the blood-prothrombin concentration was falling once more. At this point a second injection of 1 c.c. of the water-soluble compound again produced a rapid rise in blood-prothrombin concentration and a normal level was observed in sixteen hours. This level was not maintained and twenty-two hours after the second injection the blood-prothrombin concentration had fallen to 65 per cent.

It would seem from the data presented that in this case 2-methyl-1, 4-naphthoquinone when administered orally was slowly absorbed from the alimentary tract, and reaching the liver via the portal vein a considerable proportion became available there, over a period of time, for the manufacture of prothrombin. On the other hand, when the material was given intravenously, the rise in prothrombin concentration was much more rapid, but neither so complete nor so well maintained. This would suggest that as the material is delivered directly into the systemic circulation it is rapidly and entirely distributed throughout the body fluids, and thus some part of the injectable material reaches the liver almost immediately, where it becomes available for the manufacture of prothrombin. Before reaching the liver, however, it must pass in the blood-stream through the lungs where it may, like prothrombin itself (Andrus, Lord, and Kauer, 1940), be subject to disintegration; what is left of it will then be distributed widely throughout the systemic arterial tree to all the body tissues, and a portion of the material may be excreted immediately by the kidney, cf. the intravenous administration of other vitamins (Faulkner and Taylor, 1938; Meiklejohn, 1940). Thus the amount of the material actually reaching the liver initially will in all likelihood be extremely small, and moreover is unlikely to increase as time goes on. For this reason the production of prothrombin by the liver, while rapid just after the administration of the water-soluble derivative

<sup>3</sup> We thank the Abbott Laboratories, North Chicago, Illinois, for their kindness in providing us with a supply of this material.

of naphthoquinone, cannot be sustained on account of the lack of further supply such as we believe is available following oral administration of 2-methyl-1, 4-naphthoquinone and its subsequent gradual absorption from the alimentary tract.

In the treatment, therefore, of haemorrhagic hypoprothrombinaemia, intravenous administration of 'synthetic vitamin K' is recommended as the initial emergency therapeutic measure to raise as rapidly as possible the blood-prothrombin concentration above the critical level. For maintenance thereafter of a normal blood-prothrombin level, oral administration of vitamin K analogues is the method of choice.

### *Summary*

1. Observations are reported on a haemorrhagic diathesis distinct from scurvy which occurred in a patient with idiopathic steatorrhea. This haemorrhagic condition was due to hypoprothrombinaemia as a result of vitamin K deficiency and was corrected by the administration of 'synthetic vitamin K'.

2. Data are presented which suggest that while intravenous administration of 'synthetic vitamin K' in this condition produces an almost immediate and rapid rise in blood-prothrombin concentration, which is not well maintained, oral administration of an identical dose of the material causes a more gradual and less transient response.

3. *In vitro* experiments indicate that simple addition of 'synthetic vitamin K' to plasma has no effect in raising a reduced prothrombin concentration, and does not retard the disintegration of prothrombin which occurs on exposure to temperature of 37.8° C.

4. A collection was made from the literature of cases similar to the one reported above, and data on these are presented, together with the concepts of the aetiology of the haemorrhagic condition held by previous investigators. From a study of these case reports and from the authors' own observations on numerous patients with hypoprothrombinaemia, the picture of haemorrhagic hypoprothrombinaemia is drawn. The salient features of this condition are 'needle-puncture' and other subcutaneous haematomata, persistent haemorrhage from wounds, haemorrhages from the mucous membranes, and occasionally haemarthroses. Laboratory studies show a markedly reduced blood-prothrombin concentration (below 20 per cent. of normal) and some prolongation of the blood coagulation time, which is rarely extreme.

5. Haemorrhagic hypoprothrombinaemia appears in steatorrhea only after prolonged treatment with almost complete restriction of fatty foods, which greatly diminishes the intake of the fat-soluble vitamin K. It is advisable to supplement such therapeutic alterations in diet with maintenance doses of vitamin K or one of its analogues. One mg. of 2-methyl-1, 4-naphthoquinone daily by mouth was found adequate in the case reported.



We wish to thank Dr. Chester S. Keefer, under whose care this patient was admitted, for his advice, criticism, and suggestions, and for permission to publish a report on the case, and we express our gratitude to Dr. George R. Minot for his criticism and advice in the preparation of the paper.

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## HAEMORRHAGIC DIATHESIS IN IDIOPATHIC STEATORRHOEA 261

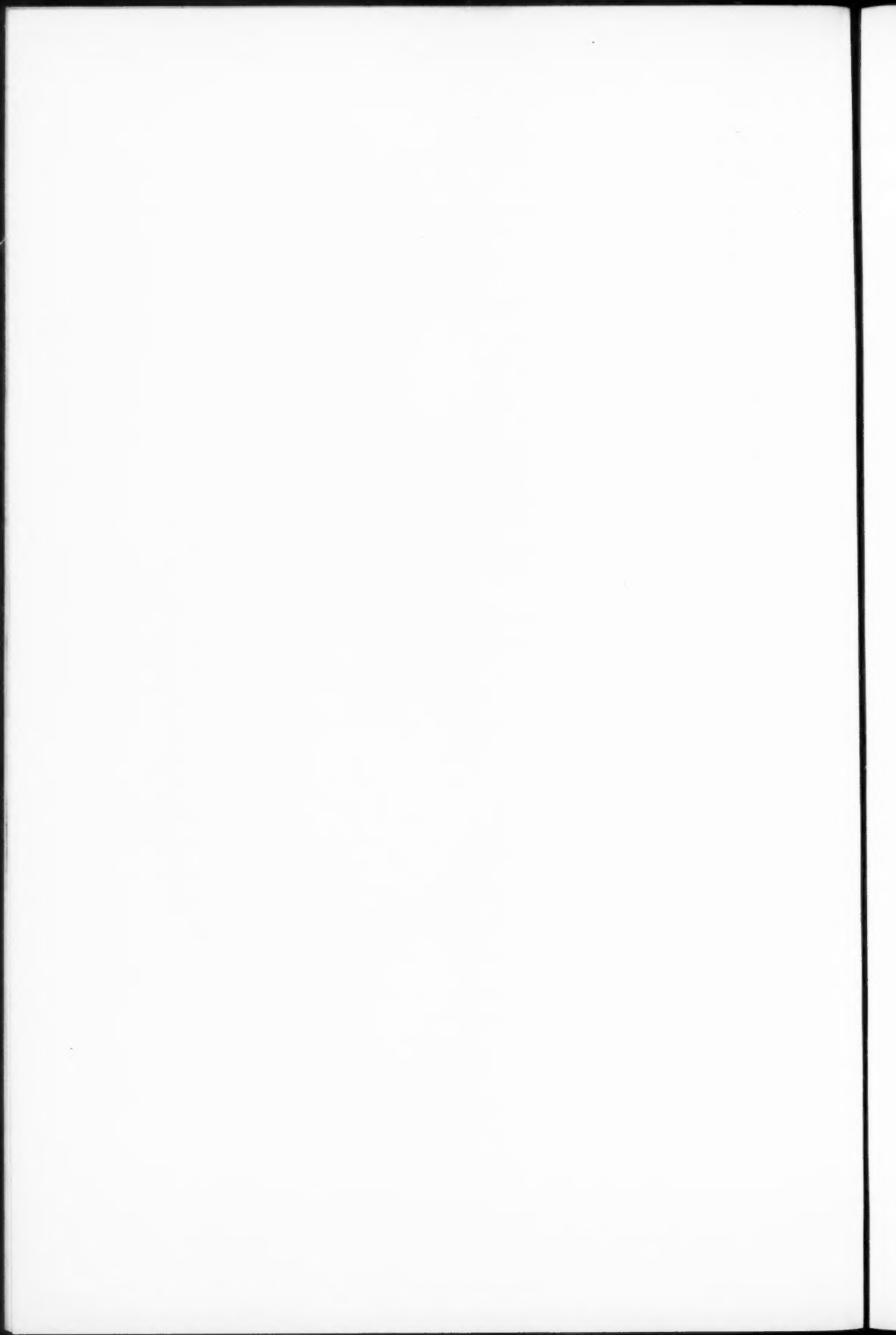
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RETINITIS PIGMENTOSA<sup>1</sup>

By E. CUNNINGHAM DAX

With Plate 16

OF the various aspects of retinitis pigmentosa that dealing with the genetics of the affection has been most fully investigated (Nettleship, 1907; Usher, 1914). A growing field of study in recent years has led to the description of many associated lesions, and in particular to the clear recognition of the Laurence-Moon-Biedl syndrome. The allied conditions are not so well appreciated, and although some have neurological components, an adequate classification has not yet been undertaken. The least success has attended biochemical studies, and with the exception of a comparatively small amount of work on the Laurence-Moon-Biedl syndrome the results have been largely negative. Some interest is therefore attached to Zondek's (1933) demonstration of disturbances in the water-salt metabolism and specific dynamic action of protein in some apparently uncomplicated cases of retinitis pigmentosa, to Nagayama's (1936) discovery of a thyrotrophic substance in the urine, and the writer's (1938) finding that the blood and urine in this condition had a melanosome-dispersing action on the skin of the frog. The present study is largely concerned with the clinical pathology of the affection, particularly from the point of view of abnormalities which might be attributed to diencephalic disturbance.

*Genetics.* Bell (1922) collected from the literature a large number of family histories of cases of retinitis pigmentosa, and these have formed the basis of most of the investigations into the mode of transmission of the condition. A new outlook was introduced in 1936 by Haldane's hypothesis of partial sex linkage, and this has been amplified and criticized in part by Burks (1937). Wibaut (1931) assumed, from a study of the disease in Holland, that genetically there were several independent recessive forms of retinitis pigmentosa, each determined by special genes. From Bell's collected cases he distinguished nine such groups, apart from those families in which the condition was a dominant or a simple recessive, and he classed a further number together which did not belong to any of these forms. In general he concluded that the dominant was a special form of the degeneration, and that when associated abnormalities were present the condition was usually a recessive. It is now generally agreed that the Laurence-Moon-Biedl syndrome fulfills the characteristics of a rare recessive.

*Associated abnormalities.* In considering some of the large number of associated defects which have been described, it is important to bear in

<sup>1</sup> Received May 15, 1940.

mind that in more than two-thirds of the cases of retinitis pigmentosa collected by Bell no associated abnormality was noted either in the affected persons or their relatives.

Deafness or deaf-mutism is the most commonly associated defect. Nettle-ship (1907) found from the literature that 4 per cent. of 1,228 deaf-mutes had retinitis pigmentosa. Lee (1883), quoted in these figures, found six examples among 110 deaf-mutes, and he also mentions two series from Hartman in which the percentages were 5.8 and 1. Vogelsang, Reich, and Barth (1937) describe cases showing the association between heredo-degenerative ear disease, pigmentary retinal degeneration, and hereditary feeble-mindedness. A number of such defectives would have to be considered in the group of deprivation amentia. Oliver (1913) described a case of retinitis pigmentosa with deafness, mental deficiency, epilepsy, and stammer. From Bell's note on the Usher pedigrees it appears that deafness would be even more frequently noted if it were specially inquired for, particularly when there is already one example of deafness and pigmentary retinal degeneration in the family.

The incidence of mental defect is greater both in the patients with retinitis pigmentosa and in their relatives than among the general population, but in the reported cases the degree of amentia is rarely described. Schleich (1885) examined the eyes of 156 'idiots' (defectives) without finding a single case of congenital blindness or retinitis pigmentosa. In 1886 he failed to find any fundus abnormalities in 127 epileptics in the same institution. The cases described in this communication represent 1 per cent. of the 1,200 defectives examined, and other fundus abnormalities were remarkably frequent.

Posterior cortical cataract is sufficiently common to be classed as a dependent rather than an associated abnormality, whilst nystagmus is also frequently found in these cases. Myopia has often been recorded and a number of cases of glaucoma have also been mentioned.

Malformed teeth (Dean, 1900), meningocele, cutaneous pigmentation, and obesity (Casini, 1935), epilepsy (Oliver, 1913), paraplegia (Hutchinson, 1900), cerebellar ataxy (Rea, 1938; Stewart, 1937), and ectopia lentis and corectopia (Derigs, 1882; Usher, 1914) are amongst the recorded conditions relevant to those found in these patients.

The Laurence-Moon-Biedl syndrome (retinitis pigmentosa, obesity, hypogenitalism, polydactyly, and mental deficiency) has now been frequently recorded, and the literature has been reviewed by Cockayne, Krestin, and Sorsby (1935) and again by Sorsby, Avery, and Cockayne (1939). They described further cases, recorded a large number of associated defects, and gave a description of some allied conditions, a number of which have some signs in common with the following cases.

*The relationship between retinitis pigmentosa and the diencephalon.* It is probably true that the tendency to associate retinitis pigmentosa with pituitary abnormalities or diencephalic disturbance arose only after the Laurence-Moon-Biedl syndrome became well known. Since the hypogenitalism and obesity

in the syndrome were identified with abnormalities of this region it was a reasonable supposition that the eye condition might be due to a like disturbance. The common developmental origin of the optic vesicles and the diencephalon, which had been noted by Dean (1900), was further evidence in favour of this hypothesis. Zondek (1935), in particular, has stressed a relationship between diencephalic disturbance and retinitis pigmentosa. He believes that abnormal hormonal influences from the pituitary body are probably produced by some interference in its co-ordination with the hypothalamus, resulting in the eye condition, and that the pathological findings originate from a systemic destruction based on an inherited predisposition. Zondek and Koehler (1932) give evidence that cases of pigmentary degeneration of the retina without other abnormal clinical signs exhibit characteristics of diencephalic disturbance, referring to work of Zondek quoted by him later (1933). They supposed that in juvenile amaurotic idiocy there was evidence of relationship of the same nature, regarding the fundus lesions in this condition as an atypical form of pigmentary degeneration of the retina. Velhagen (1932) gives evidence to support this hypothesis.

Zondek (1935) has used prolactin with some improvement of the symptoms in retinitis pigmentosa, and Viallefont (1936) describes the treatment of four cases with an extract of whole pituitary gland and cites four other accounts of cases similarly treated. Italian writers support the endocrine origin of retinitis pigmentosa, but do not limit it to a diencephalo-hypophyseal disturbance; they mainly stress an associated vascular factor (Farina, 1936; Mecca, 1936; Rinaldi, 1937; Schupfer, 1937). Four of Mecca's five patients exhibited abnormalities of the sella turcica. Migraine occurred in two of them and also in an affected brother of one of these. Ovarian insufficiency was seen in three of the cases.

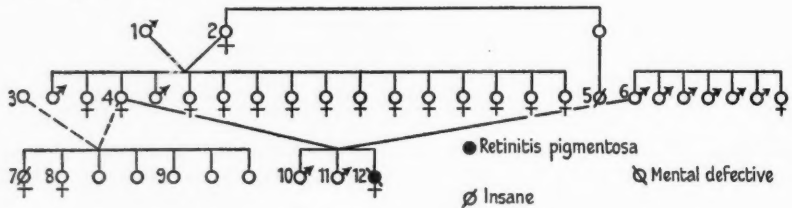
Nagayama (1936) determined the action of the morning urine of six patients with retinitis pigmentosa on the follicles of the thyroid in rabbits by injecting the urine into the circulation and examining the thyroid histologically. He found thyrotrophic substances in the urine of the patients, but not in that of the controls. The writer injected prepared specimens of blood and urine from cases of retinitis pigmentosa into the dorsal lymph sac of frogs, and so produced a melanosome-dispersion as seen by the darkening of the animals' skin.

Vercelli (1938) describes myoclonic epilepsy, other neurological signs, and metabolic evidence of a diencephalo-hypophyseal complex in a patient with retinitis pigmentosa. Wolff (1938) investigated two patients with the Laurence-Moon-Biedl syndrome. He found evidence of disturbance of the hypophysis or hypothalamus, which he believes may be of cerebral origin, as shown by abnormalities in the water excretion and the specific-dynamic action of protein.

*Case Reports*

*Case I.* A typical example of the Laurence-Moon-Biedl syndrome, showing mental defect, hypogenitalism, polydactyly, obesity, and retinitis pigmentosa. A previous description of this patient, with photographs, was given by Klenerman (1935).

Born 1882; admitted 1922.

*Family history.*

1—died aged 95 years. 2—died in early middle life, cause unknown. 3—the patient's mother's first husband. 4—the mother; died in 1909, aged 73 years. The informant said the cause was senility, but from another source it was reported to be from 'paralysis of the brain'. 5—a maternal cousin, who was insane. 6—the father, whose place in his family is not known. 7—said to have been insane after being hit with a hammer in 1900, but not certified until 1929, and died in 1933 in a mental hospital. 8—normal. 9—had five children, sex not known, who died in infancy or early childhood. 10—the informant, intelligent and normal, married, but with no children. 11—died by choking in his first year. 12—the patient.

Nothing further is known of the maternal or paternal siblings or their families, but the informant is sure he would have heard of any abnormalities. The mother and father were not related before marriage.

*Past history.* Her birth was normal, but she was born with webbed fingers and supernumerary digits on both hands and one foot. She was always excitable, but not thought to be backward, and is said to have talked at the same time as other children. When aged about three years she had a finger removed from each hand, and after her return from hospital it is said that she began to scream incessantly. About the age of four or five years her sight began to fail, and she was transferred to a school for the blind, and then to Leavesden Hospital when aged 18 years. The first hospital record found was in 1922 when she was noted as being blind, faulty, and requiring every attention. Her mental age was 4·2 years.

*Present condition.* She is a simple childish imbecile, amusing to both patients and staff, placid and good tempered. She makes no attempt to employ herself in any useful way. She has no perception of light now, though she does not appear to have been absolutely blind a few years ago. The periphery of her fundi can just be seen, and dense retinal pigmentation is obvious, but no details can be made out. There are dense striae and opaque nuclei in both lenses. There is a rotatory nystagmus. The pupils are equal and circular. The irides are grey-blue with some brown speckling medially. She is very obese, particularly about the body. Both her legs and arms are rather fat, but the hands, wrists, feet, and ankles are quite



small. As long ago as 1925 it was suspected that she had an ovarian cyst; her girth in 1935 was 53 in. She always holds her arms flexed and internally rotated with her thumbs in her palms. There are six digits on the right hand with syndactyly between the middle and the double ring-finger which has two nails. On the outer sides of both hands there are scars where a digit has been removed. There are five digits on the left hand. On the left foot there are six regular toes, on the right foot five. There is no spinal curvature. The skin is smooth and the hair normal. Pulse rate 70 to 90 taken four-hourly over ten days. Blood-pressure at various times in the last ten years was 135/115, 200/108, 196/104, 190/100. The heart and blood vessels show no gross abnormality. There is a little chronic bronchitis. Other than the enlargement there is nothing to be found on palpation of the abdomen. The only abnormality of the central nervous system is a continuous slight side to side movement of the head, and a regular forward jerk. She has rarely complained of headaches. Her breasts are normal, and axillary and pubic hair are present. There is no record of her ever having menstruated whilst in hospital, and her brother does not know of her having done so.

#### Investigations:

##### *Craniometry.*<sup>2</sup>

Distance between inner canthi . . . . .	2.4 cm.
Mean breadth of palpebral fissures . . . . .	2.65 cm.
Ear breadth . . . . .	13.2 cm.
Maximum breadth . . . . .	13.9 cm.
Breadth index . . . . .	95
Anterior length . . . . .	10.3 cm.
Maximum length . . . . .	18.1 cm.
Length index . . . . .	57
Cephalic index . . . . .	77
Height . . . . .	12.9 cm.
Circumference . . . . .	52.5 cm.
Capacity—Lee's formula . . . . .	1233 c.c.
Penrose's formula . . . . .	1200 c.c.

X-rays of the skull show the pituitary fossa to be on the large side. The sinuses are normal. The tables of the skull are rather thick and dense.

<sup>2</sup> The distances between the inner and outer canthi were measured with engineer's callipers, and the mean palpebral breadth is half the difference between them. The ear breadth is the distance between points immediately in front of the pinna and above the zygoma of either side. The maximum breadth is the greatest distance between symmetrical points on either side of the skull above the external auditory meatus, and the maximum length is the greatest measurement from the glabella to a point at the back of the head in the mid-line. These three measurements were made with a craniometer. The anterior length is the distance of the glabella from a line which would run through the external auditory meatus of either side. The height is measured from this line to a point on top of the head in the mid-line, at right angles to the Frankfort line (which is drawn through the lower margin of the orbit and the external auditory meatus). The circumference is the maximum distance round the head when the tape is symmetrical on the two sides and crosses the glabella. Two formulae for cranial capacity are given. Lee's is calculated from the length, breadth, and height, and Penrose's is an approximation from the length and breadth. Thus if the height is greater than would be anticipated from the length and breadth the figure given by Lee's formula is the greater and vice versa. The normal values of the length, breadth, and cephalic indices are 53 to 58, 85 to 90, and 75 to 80 respectively. All the cases described have been measured in the same way.

X-rays of the right hand show a small spicule of bone  $\frac{1}{8}$  in. long arising from the middle of the fifth metacarpal and three terminal phalanges of the middle and ring fingers, which are fused together. The left hand shows a rudimentary accessory third phalanx between those of the middle and ring fingers. The left foot shows the little toe to have two terminal phalanges, two middle phalanges, and two heads to a common metatarso-phalangeal bone. The X-ray of the right foot is normal.

Height 61 in. Span  $60\frac{1}{2}$  in. Pubis-vertex 33 in. Pubis-feet 28 in. Her weight was 12 st. in 1923 and 8 st. in 1926, the loss being unexplained; it increased to 16 st. in 1936 and has since been 14 to 15 st. For the past three years there has been a fluctuation between winter and summer weights of about 13 lb. The temperature was taken by the mouth four-hourly for ten days and found to be normal with the exception of two consecutive readings of  $99.4^{\circ}$  and  $98.6^{\circ}$  F.

A blood-count showed—red cells 4,900,000 per c.mm.; haemoglobin 94 per cent.; colour index 0.95; white cells 9,350 per c.mm.; polymorphs 51.5, lymphocytes 46, monocytes 0.5, eosinophils 1.5, and basophils 0.5 per cent. A previous blood-count in 1934 was very similar, the lymphocytes being 51.5 per cent. of 7,500 white cells.

Serum-calcium 9.9 mg. per 100 c.c., plasma-phosphate 3.45 mg. per 100 c.c., plasma-cholesterol 203 mg. per 100 c.c., blood-urea 37.5 mg. per 100 c.c., urea clearance 80 per cent. of normal.

Glucose tolerance curves:

	1931.	1937.	1938.
0 hrs. . . .	116 mg. %	240 mg. %	236 mg. %
$\frac{1}{2}$ " . . .	124 "	230 "	234 "
1 " . . .	145 "	443 "	236 "
$1\frac{1}{2}$ " . . .	162 "	400 "	236 "
2 " . . .	140 "	375 "	224 "

Urine: pale yellow, S.G. 1011, acid reaction, sugar +++, no acetone bodies, no phenylpyruvic acid, numerous leucocytes. In 1933 there was no glycosuria; in 1936 much sugar, but no acetone, was found. She has not had any treatment. Diastatic index, 10 units.

Water-salt metabolism:

*Water Intake and Output for One Week in 1937.*

Intake.		Output.	
Fluid	Solid	Urine	Faeces
385	128	344	33
513 oz.		377 oz.	

This is within normal limits.

In 1931, 36 oz. of urine were passed in 24 hours. In 1938, after four days on a constant diet of low chloride content, the following figures were obtained:

	Urinary volume.	Sodium chloride.
5th day . . .	1818 c.c.	5.63 gm.
6th " . . .	2212 "	6.43 "
7th " . . .	2268 "	6.02 "
8th " . . .	2320 "	9.65 "
9th " . . .	2430 "	9.96 "

Ten grams of sodium chloride were given on the eighth morning. There was no chloride retention.

## Urine dilution test:

<i>Time.</i>	<i>Urinary volume.</i>
6.35 a.m.	70 c.c.
8.0 "	500 "
8.40 "	150 "
9.25 "	190 "
11.0 "	50 "

1,000 c.c. of water were given between 6 and 6.30 a.m. This was a diminished output and a delayed secretion, the rate being less than normal.

Melanosome dispersion by the urine has been observed, the results often being strongly positive. It has also been produced by the blood. The cerebrospinal fluid was not tested.

Loewi's eye test: The pupils became markedly dilated transversely, with some eccentricity.

## Vitamin C excretion:

	<i>November 1938.</i>	<i>December 1938.</i>
1st day . . .	22-30 mg.	23-13 mg. ascorbic acid
2nd " . . .	23-90 "	26-30 " "
3rd " . . .	24-18 "	29-20 " "

The second results were after a month's feeding of 50 mg. of ascorbic acid daily. On each occasion 300 mg. of ascorbic acid were given on the third morning. There was a gross vitamin deficiency.

Head nodding in the Laurence-Moon-Biedl syndrome has been previously recorded by Deusch (1925) and Paton (1936).

*Case II.* An example of the Laurence-Moon-Biedl syndrome without hypogenitalism. The case has been described by Klenerman (1935) with a photograph.

Born 1862; admitted 1892. She has no relatives and is incapable of giving an account of the family history herself.

*Past history.* Nothing is known of her early life. In 1909 her eyesight was noticed to be failing, in 1916 she bumped into furniture and doors. The following year she was described as being blind. She was generally diagnosed as feeble minded with superimposed dementia praecox. In 1916 she was said to be a chronic grumbler who was deluded that her food was poisoned. Ten years later she thought herself to be watched. She rambled in conversation, was quarrelsome, interfering, and easily provoked to anger.

*Present condition.* She is becoming demented. She sits beside the fire, talking to herself about her past life in the hospital. She answers questions in a rambling fashion, dislikes interference, but is happy, clean, and not difficult to manage. She has no perception of light, and dense cataracts make only the periphery of the fundi visible, where much pigment is to be seen. Two years ago much more of her fundi could be examined. There is a rapid lateral nystagmus. The pupils are equal, small and round, and dilate equally with atropine. Her irides are blue-grey. There is a marked arcus senilis. Her skin is very lax and dry, but she has lost much weight. Her hair is thick and dry. She has some acromegalic characteristics, a protruding lower jaw, splayed nostrils, and heavy, blunt features. She has a marked degree of dorsal kyphosis which was painful in 1936, and a slight

degree of right-sided scoliosis and lumbar lordosis. She has long legs and arms and a rickety chest. Her digits are of normal size, except that the second toes are longer than the first, and there is a slight webbing between the second and third toes on either side. There is a supernumerary small toe on her right foot. She has myocardial degeneration, and a moderately dilated heart. Her brachial arteries are hard, thick, and tortuous. Her blood-pressure is 105/75. She has chronic bronchitis and emphysema. Her tongue shows marked venous dilatation about the edges. Her abdomen is protruberant without being found to be abnormal. Other than a shaking of her hands and a tremor of her tongue, her nervous system is normal. For many years she has complained of headaches behind the right eye.

*Investigations:*

*Craniometry.*

Distance between inner canthi . . . . .	3.6 cm.
Mean breadth of palpebral fissures . . . . .	2.45 cm.
Ear breadth . . . . .	12.7 cm.
Maximum breadth . . . . .	14.3 cm.
Breadth index . . . . .	89
Anterior length . . . . .	10.4 cm.
Maximum length . . . . .	19.7 cm.
Length index . . . . .	53
Cephalic index . . . . .	73
Height . . . . .	13.5 cm.
Circumference . . . . .	55.8 cm.
Capacity—Lee's formula . . . . .	1424 c.c.
Penrose's formula . . . . .	1400 c.c.

On X-ray examination the pituitary fossa was moderately enlarged. The sinuses were small, but the skull was rather thick. There was an over-sliding of the occipital bone on the parietals (a condition the writer has seen in three other defectives).

The X-ray of the right foot showed the little toe to have two independent terminal phalanges and a bifid second phalanx attached to a single metatarsophalangeal bone. The left foot and hands were normal except for osteoarthritic changes.

Height 56½ in. Span 63 in. Pubis-vertex 27 in. Pubis-feet 29½ in. Her weight is now 7 st. 11 lb., in 1926 it was 10 st. 7 lb. It has fluctuated a great deal in the past 15 years. The temperature was normal taken four-hourly for ten days both by the mouth and rectum. There was less difference between the two readings than is usually seen.

A blood-count showed—red cells 4,830,000 per c.mm.; haemoglobin 93 per cent.; colour index 0.96; white cells 6,750 per c.mm.; polymorphs 61, lymphocytes 31, eosinophils 3.5, and monocytes 4.5 per cent. In 1932 a blood-count gave almost identical figures.

Serum-calcium 10.2 mg. per 100 c.c., plasma-phosphate 3.75 mg. per 100 c.c., plasma-cholesterol 245 mg. per 100 c.c., blood-urea 37.5 mg. per 100 c.c., urea clearance 70 per cent. of normal.

Glucose tolerance curves:

	1932.	1933.
0 hrs. . . . .	93 mg. %	95 mg. %
½ " . . . . .	169 "	175 "
1 " . . . . .	242 "	250 "
1½ " . . . . .	154 "	230 "
2 " . . . . .	98 "	168 "

Urine: pale yellow, S.G. 1011, neutral reaction, a trace of albumin, but no sugar, acetone, or phenylpyruvic acid was present. Many leucocytes and organisms present. In 1932 there was a heavy infection, but no albumin was reported.

Water-salt metabolism:

<i>Water Intake and Output for One Week in 1937.</i>			
<i>Intake.</i>		<i>Output.</i>	
Fluid	Solid	Urine	Faeces
387	114	320	6
501 oz.		326 oz.	

The output was below normal, but this was probably due to constipation.

After four days on a constant diet of low chloride content, the following figures were obtained:

		<i>Urine volume.</i>	<i>Sodium chloride.</i>
5th day	.	1225 c.c.	2.45 gm.
6th "	.	1505 "	4.59 "
7th "	.	1270 "	3.11 "
8th "	.	1360 "	5.92 "
9th "	.	1275 "	5.04 "

Ten grams of sodium chloride were given on the eighth morning. A chloride retention of about 4 gm. was present.

Urine dilution test:

<i>Time.</i>	<i>Urinary volume.</i>
8.5 a.m.	70 c.c.
8.45 "	158 "
11.0 "	100 "

1,000 c.c. of water were given between 6 and 6.30 a.m. A gross water retention; the rate and volume are both diminished.

Melanosome dispersion by the urine has been observed a number of times. The blood and cerebrospinal fluid were not tested.

Vitamin C excretion:

	<i>November 1938.</i>	<i>December 1938.</i>
1st day	10.41 mg.	9.73 mg. ascorbic acid
2nd "	8.32 "	11.21 "
3rd "	10.03 "	14.73 "

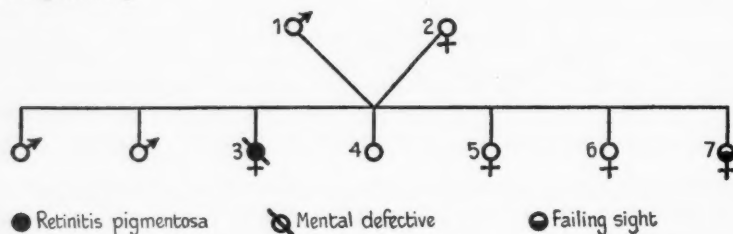
The second results were after a month's feeding of 50 mg. of ascorbic acid daily. On each occasion 300 mg. of ascorbic acid were given on the third morning. There was a gross vitamin deficiency as expected in view of her age.

A case of the Laurence-Moon-Biedl syndrome described by Sorsby, Avery, and Cockayne (1939) was obese, but later became thin. The loss of weight appeared in adolescence, whereas here it was not marked until the patient became old.

*Case III.* An example of the Laurence-Moon-Biedl syndrome, without polydactyly, but with short arms and legs.

Born 1886; admitted 1921.

*Family history.*



1—the father, died aged 74 years from a stroke. 2—the mother, died aged 67 years from pneumonia. They were not related before marriage. 3—the patient. 4—died in infancy, sex not known. 5—died aged 45 years from carcinoma of the breast. 6—the informant, who is illiterate, lives in America, and was unable to give fuller details than these. 7—born in 1897, is said to look just like the patient, and to have poor vision.

*Past history.* Birth normal; it is said that she walked, talked, and was clean at the usual times, but when she was five she was noticed to be backward. She attended school. Her sight was first noticed to be failing when she was aged 31 years, but on admission four years later she was nearly blind. In spite of her failing sight she has been anxious to help and willing to polish, and has treasured beads and ribbons.

*Present condition.* She is a childish, simple imbecile, always well-behaved, willing, amusing, likeable, and never upset. Her vision has been very poor since admission. Though at first she appeared to be able to see a little, she now seems to be quite blind, without light perception. Her disks are white with well marked edges, the vessels are minute and can scarcely be traced into the retina. The pigment is coarse and spidery, and chiefly distributed in the circumpapillary area, but is also seen in the equatorial and peripheral areas. On three occasions in 1938 and 1939 she had injections of Kiton fast green, twice intramuscularly and once intravenously. On the last occasion 65 c.c. of a 10 per cent. solution of the dye were given without ill-effect, and by this means it was found that during the preceding year the condition had shown marked progress (Sorsby, 1939). The right macular region stained less than the remainder of the fundus, and on the left side the macula was the only portion spared from a marked staining, though the colouring was more patchy than in the right eye. There is a lateral nystagmus. The pupils are equal and circular. Her irides are similar and grey in colour with some brown speckling. The eyes are rather small, deeply set, and slit-like. In 1934 she complained of photophobia, and now she keeps the eyes closed, resists opening, and lachrymates freely on examination. Posterior cortical cataracts seen two years ago are now increasing.

Her face is plump and is very little lined, she has a high colour and is very freckled. Her skin is soft and smooth, but her hair is black and wiry. She is obese and the fat is centrally distributed. Her arms and legs are short compared with her trunk, and comparatively thin. Her feet are



broad and her toes are in proportion; her hands also are inclined to be broad and the fingers stumpy. Her spine is normal and there is no polydactyly. Her palate is normal, but her ears are small with adherent lobules, and there is slight webbing between the second and third toes of both feet. Her pulse for ten days was between 75 and 80. Her blood-pressure (155/100) has been about the same for the past five years. The vessels and heart are normal. There are no signs of vasomotor disturbance. Since 1932 she has vomited from time to time with increasing frequency, but until recent months there has been no loss of weight and no pain. Her appetite has always been very good. Recently she has vomited changed blood. An X-ray of her gastrointestinal tract was negative. Three months of ulcer diet has relieved the pain and vomiting, but she is thinner. She has had bad headaches on and off for years, but is incapable of describing them, though at these times she screws up her eyes. The only abnormalities of her nervous system are rather sluggish reflexes, nystagmus, ptosis, and pupils which do not react to light. Her genitalia are very small, and she has little hair on her pubis or in her axillae. Menstruation was scanty.

#### *Investigations:*

##### *Craniometry.*

Distance between inner canthi . . . . .	2.8 cm.
Mean breadth of palpebral fissures . . . . .	2.75 cm.
Ear breadth . . . . .	12.5 cm.
Maximum breadth . . . . .	14.1 cm.
Breadth index . . . . .	89
Anterior length . . . . .	9.6 cm.
Maximum length . . . . .	17 cm.
Length index . . . . .	56
Cephalic index . . . . .	83
Height . . . . .	12.1 cm.
Circumference . . . . .	50.6 cm.
Capacity—Lee's formula . . . . .	1115 c.c.
Penrose's formula . . . . .	1110 c.c.

X-rays of the skull show the pituitary fossa to be of normal size, but the skull is rather thin and dense and the sinuses small. X-rays of hands and feet showed no abnormality.

Height  $56\frac{1}{2}$  in. Span 53 in. Pubis-vertex 30 in. Pubis-feet  $26\frac{1}{2}$  in. Her weight was 11 st. 13 lb. in 1922, 10 st. 8 lb. in 1928, 11 st. 10 lb. in 1931, and 12 st. 6 lb. in 1933, but has dropped to 10 st. since she has had gastric symptoms. The temperature was normal, measured by the mouth four-hourly for ten days.

A blood-count showed—red cells 5,010,000 per c.mm.; haemoglobin 91 per cent.; colour index 0.91; white cells 6,450 per c.mm.; polymorphs 32, lymphocytes 65.5, monocytes 0.5, eosinophils 1.5, and basophils 0.5 per cent.

Serum-calcium 11.6 mg. per 100 c.c., plasma-phosphate 4 mg. per 100 c.c., plasma-cholesterol 208 mg. per 100 c.c., blood-urea 38 mg. per 100 c.c., urea clearance 65 per cent. of normal in 1935.

Urine: yellowish-red in colour, S.G. 1027, acid reaction, deposit of urates, no abnormal constituents, and no phenylpyruvic acid. Diastatic index 28.5 units.

Water-salt metabolism: After four days' feeding on a constant diet of low chloride content, the following figures were obtained:

		Urine volume.	Sodium chloride.
5th day	. .	1633 c.c.	4.57 gm.
6th "	. .	1661 "	3.99 "
7th "	. .	1576 "	5.43 "
8th "	. .	1540 "	9.63 "
9th "	. .	1810 "	7.78 "

Ten grams of sodium chloride were given on the eighth morning. There was no chloride retention.

Urine dilution test:

Time.	Urine volume.
7.0 a.m.	100 c.c.
7.30 "	300 "
8.0 "	260 "
8.45 "	300 "
9.35 "	200 "
10.20 "	110 "
11.0 "	40 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The rate of secretion was normal, but there was slight delay in excretion. The volume was normal.

Melanosome dispersion by the urine has been observed on a number of occasions, and also by the blood, but not by the cerebrospinal fluid.

Loewi's eye test gave a strongly positive result. In less than half an hour the pupils became elliptical and dilated in an oblique axis with marked eccentricity.

Fractional test meal:

Time	0	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	1	$1\frac{1}{4}$	$1\frac{1}{2}$	$1\frac{3}{4}$	2	$2\frac{1}{4}$ hrs.
Free HCl	29	—	4	14	31	37	20	34	40	35 c.c. N/10 NaOH
Total acidity	39	13	38	50	53	51	50	59	59	59 " " "

Starch was still found at the end of this time and no bile was present. Occult blood has been found in the stools on several occasions.

Vitamin C excretion:

	November 1938.	December 1938.
1st day	11.34 mg.	16.74 mg. ascorbic acid
2nd "	15.90 "	17.25 "
3rd "	16.28 "	34.13 "

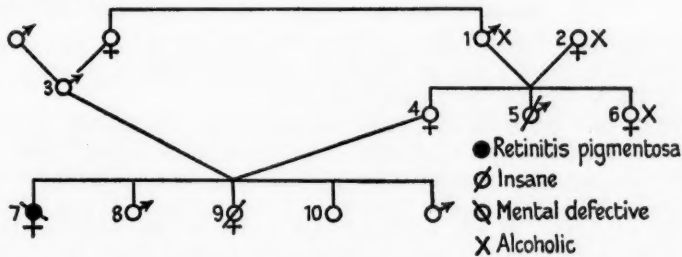
The second results were after a month's feeding of 50 mg. of ascorbic acid daily. On each occasion 300 mg. of ascorbic acid were given on the third morning. The vitamin excretion was normal compared with the controls.

Casini (1935) recorded a case with retinitis pigmentosa, obesity, pigmented skin with much freckling, and meningocele. This case has retinitis pigmentosa, obesity, freckling, and hypogenitalism.

*Case IV.* Retinitis pigmentosa with mental deficiency, obesity, and microphthalmos.

Born 1900; admitted 1938.

*Family history.*



1—a chronic alcoholic. 2—a chronic alcoholic, who died from cirrhosis of the liver. 3—died aged 47 years from pneumonia. 4—born 1870, healthy; a first cousin of the father. 5—insane. 6—a chronic alcoholic. 7—the patient. 8—died aged 24 years; 'his skin went into holes'. 9—insane. 10—died aged 3 months. 11—normal and in good health.

*Past history.* She walked at 3 years, but is said to have groped her way about. She talked at the age of 3½ years, and then went to a special school. She was a timid child, who cried on the least provocation. Later she learned to read braille, but her sight could not have been very bad until after she left school, as she used to run messages at that time.

*Present condition.* She is good-tempered, placid, and is no trouble to nurse. She is facile and simple. Her mental age is 7·9 years. She spends her time threading beads and reading braille. She has only perception of light. The disks are waxy, the vessels small, and there are dense deposits of spidery pigment over most of her retinae. There is early cataract of both lenses in the form of radiating striae from the nuclei. Her eyes are small and deeply set. She has a lateral nystagmus and a slight convergent strabismus. Her irides are grey. Her skin is soft and her hair brown and fairly fine. She has a high palate and large teeth. The central incisors are notched, but wider below than above and are not round in section. She is obese about the face, chest, and abdomen, but her arms and legs are small in comparison. The hands and feet are normal. There is no spinal or other skeletal deformity. The pulse is 68 to 80, and blood-pressure 140/74. She sweats a great deal at all times. Her extremities are cyanosed. The lungs, abdomen, and thyroid appear to be normal. The reflexes are sluggish and she is partially deaf. She has had frontal headaches for some years, 'as if someone were banging her head'. Her menstruation and sex characteristics are normal.

*Investigations:*

*Craniometry.*

Distance between inner canthi . . . . .	3·1 cm.
Mean breadth of palpebral fissures . . . . .	2·45 cm.
Ear breadth . . . . .	12·8 cm.
Maximum breadth . . . . .	14·1 cm.
Breadth index . . . . .	91
Anterior length . . . . .	10·1 cm.
Maximum length . . . . .	18·0 cm.

*Craniometry (continued).*

Length index . . . . .	56
Cephalic index . . . . .	78
Height . . . . .	13.0 cm.
Circumference . . . . .	52.9 cm.
Capacity—Lee's formula . . . . .	1252 c.c.
Penrose's formula . . . . .	1210 c.c.

X-rays of the skull show no abnormality. The sesamoids are prominent and there are two of these bones in abnormal positions in the feet, otherwise the X-rays of the hands and feet are normal.

Height 60 in. Span 60 in. Pubis-vertex 31 in. Pubis-feet 29 in. Her weight was 8 st. 7 lb. on admission, and 11 st. 8 lb. a year later. It is probable that she was suffering from gross malnutrition, and that treatment of this is the only cause of the increase. The temperature was taken four-hourly for six days. It was normal in the axilla for the first two days, but taken by the mouth on the other four days it reached 99.6°, 99°, 98.8°, and 100.8° F.

A blood-count showed—red cells 4,110,000 per c.mm.; haemoglobin 87 per cent.; colour index 1.06; white cells 6,650 per c.mm.; polymorphs 65, lymphocytes 29, monocytes 3, and eosinophils 3 per cent.

Serum-calcium 10.2 mg. per 100 c.c., plasma-phosphate 3.54 mg. per 100 c.c., plasma-cholesterol 216 mg. per 100 c.c.

Urine: acid reaction, S.G. 1020, no abnormal constituents, and no phenylpyruvic acid.

Water-salt metabolism: After four days' feeding on a constant diet of low chloride content, the following figures were obtained:

	<i>Urine volume.</i>	<i>Sodium chloride.</i>
5th day . . . . .	1030 c.c.	2.99 gm.
6th " . . . . .	950 "	5.13 "
7th " . . . . .	1688 "	12.77 "
8th " . . . . .	1550 "	8.68 "

Ten grams of sodium chloride were given on the seventh morning. There was no chloride retention.

## Urine dilution test:

<i>Time.</i>	<i>Urine volume.</i>
7.30 a.m.	240 c.c.
8.0 "	210 "
8.30 "	85 "
9.0 "	120 "
9.30 "	110 "
10.0 "	180 "
10.30 "	110 "
11.0 "	45 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The curious lag in the rate of secretion between 8 a.m. and 9 a.m. was confirmed in a repetition of the test. There was a normal rate of secretion and volume, but a delay in output.

Melanosome dispersion by the urine was not observed on the only two occasions on which it was attempted.

Cavallacci (1937) described hypophyso-hypothalamic disturbances associated with microphthalmos and cataract in three patients whom he compared with the Laurence-Moon-Biedl syndrome. This patient has obesity, microphthalmos, cataract, and retinitis pigmentosa.

*Case V.* A case of familial cerebellar hypoplasia, mental deficiency, retinitis pigmentosa, and hypogenitalism. She has been recorded by Stewart (1937).

Born 1909; admitted 1910.

*Family history.* (See pedigree diagram on p. 279.)

1—normal sight. 2 and 3—normal sight. 4—died aged 69 years, healthy. 5—died aged 70 years, healthy. 6—died aged 69 years, stricture. 7—large, healthy family. 8—died aged 63 years of heart failure. 9—born 1862; not related to his wife before marriage; undersized; was an alcoholic; colour-blind, but says there were no other cases in his family. Nothing wrong with the sight of any of his nieces and nephews. 10—born 1870; partially deaf; 'nervy', and has severe frequent headaches. There has never been any abnormality in her family and her nieces and nephews are all healthy. 11—died aged 24 years of pneumonia. 12—died of tuberculous shoulder. 13—born 1894; tuberculosis as a child; healthy since she was 21 years. 14—born 1896; died of meningitis, aged 2 years. 15—born 1900; infantile paralysis when 2 years, now married. 16—born 1903; died in Leavesden Hospital in 1937; she was extremely like the patient in every way; she did not walk or talk; an autopsy verified the diagnosis. 17—born 1905; normal. 18—the patient. 19—born 1911; normal.

*Past history.* No abnormality was noticed until she was 3 months old, when she looked similar to her sister and was admitted to hospital when a year old. Her sight was then normal.

*Present condition.* She is a low-grade imbecile, but is able to feed herself. She is sometimes incontinent of urine at night. She is contented, but shows some emotional instability. She gives monosyllabic replies to simple questions. She does nothing but play with bricks and beads. Her disks are waxy, the vessels are small, and spidery pigment is to be seen in the equatorial region and peripherally. A few wisps are just visible in the central areas. There are some rather woolly linear deposits along some of the veins. Her lenses are clear. The irides are grey-blue in colour. She appears to be night-blind and to have some considerable field limitation, but it is difficult to be sure in her case. Her vision is sufficiently good to see movements of the hand eight yards away. The skin is soft and smooth, the subcutaneous fat is normal in amount, the palate is high but not narrow, the ears are pointed and the lobules are absent. The hair is coarse and ginger in colour. The teeth are sound but uneven. The main skeletal abnormality is a marked lower dorsal kyphosis and right-sided scoliosis with a corresponding chest deformity. Her hands and fingers are rather long and tapering. The thumbs are inclined to the simian position. The feet are short and broad and there is less difference than is usual in the size of the various toes. Laxity of the ligaments is well marked.

Her blood-pressure is 120/70, and her pulse-rate has been 60 to 80 over ten days. She has bilateral ptosis with much wrinkling of the forehead on elevation of the eyes. There is slight tremor of the tongue; emotional movements of the upper part of the face are less than is usual. Otherwise the cranial nerves are normal. Sensation is difficult to test except for pain, which is appreciated. There is general motor weakness, hypotonia, incoordination, and asynergy. There is much associated movement in attempting any action. Dysidiadochokinesis is marked, with some dysmetria on the left side, and gross ataxy of both arms and legs. There is no drooping away



of the outstretched arms, but much involuntary movement. The reflexes are inclined to be sluggish. The plantar responses are flexor, the knee jerks of the pendulum type. She is unable to stand by herself, but when supported she raises a leg high up in an attempt to walk, stamps the foot, and then follows rapidly with the other leg in an uncontrolled manner. The speech is indistinct owing to the gross muscular inco-ordination, but with practice she can be understood. There is a definite explosive quality in the sounds. She is not an epileptic, and never complains of headaches. She has never menstruated and her genitalia are small. She has a sparse growth of pubic and axillary hair, but her hips are quite prominent. Her breasts are small and symmetrical.

*Investigations:*

*Craniometry.*

Distance between inner canthi	.	.	.	3.2 cm.
Mean breadth of palpebral fissures	.	.	.	2.7 cm.
Ear breadth	.	.	.	13.1 cm.
Maximum breadth	.	.	.	14.9 cm.
Breadth index	.	.	.	88
Anterior length	.	.	.	10.2 cm.
Maximum length	.	.	.	19 cm.
Length index	.	.	.	54
Cephalic index	.	.	.	78
Height	.	.	.	13 cm.
Circumference	.	.	.	55.7 cm.
Capacity—Lee's formula	.	.	.	1382 c.c.
Penrose's formula	.	.	.	1390 c.c.

X-rays of the skull showed the pituitary fossa to be small, the skull was dense and rather thin, the tables fused, and sinuses small. The hands and feet were not X-rayed.

Height 60 in. Span 62 in. Pubis-vertex 30 in. Pubis-feet 30 in. Her weight was 7 st. 11 lb. and had been constant for some years, with little variation between summer and winter. The temperature was taken four-hourly by the mouth over ten days, and was found very constantly to be 96.2° to 96.4° F. at 10 p.m. and 2 a.m., and 98.8° to 99° F. at 2 p.m.

A blood-count showed—red cells 4,920,000 per c.mm.; haemoglobin 97 per cent.; colour index 0.99; white cells 7,600 per c.mm.; polymorphs 59, lymphocytes 32.5, eosinophils 5.5, monocytes 2, basophils 1 per cent.

Serum-calcium 10.2 mg. per 100 c.c.; plasma-phosphate 3.58 mg. per 100 c.c.; plasma-cholesterol 184 mg. per 100 c.c.

Urine: pale yellow, S.G. 1012, neutral reaction, no abnormal constituents, and no phenylpyruvic acid.

Water-salt metabolism: After four days' feeding on a constant diet of low chloride content, the following figures were obtained:

		<i>Urine volume.</i>	<i>Sodium chloride.</i>
5th day	.	1271 c.c.	5.34 gm.
6th "	.	1839 "	5.70 "
7th "	.	1371 "	3.98 "
8th "	.	1400 "	9.1 "
9th "	.	1600 "	8.08 "

Ten grams of sodium chloride were given on the eighth morning. There was no chloride retention.





## Urine dilution test :

Time.	Urine volume.
6.45 a.m.	40 c.c.
7.25 "	310 "
8.10 "	400 "
9.0 "	550 "
10.15 "	240 "
11.0 "	70 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The rate of secretion was normal, as was the volume, but there was a delay in secretion.

Melanosome dispersion has been shown by both the blood and urine, but not by the cerebrospinal fluid.

The cerebrospinal fluid pressure was not measured on a manometer, but the drops appeared rather more rapidly than usual. The constituents were normal.

Stools negative for *B. tuberculosis*.

## Vitamin C excretion :

	November 1938.	December 1938.
1st day . . .	15.23 mg.	15.26 mg. ascorbic acid
2nd " . . .	15.88 "	21.93 " "
3rd " . . .	17.69 "	18.40 " "

The second results were after a month's feeding of 50 mg. of ascorbic acid daily. On each occasion 300 mg. of ascorbic acid were given on the third morning. There was a gross vitamin deficiency.

Biamond (1934) described a patient with cerebellar ataxia, nystagmus, exophthalmos, and brachydactyly. The siblings had similar abnormalities, though none displayed the whole syndrome; one of the four had ptosis.

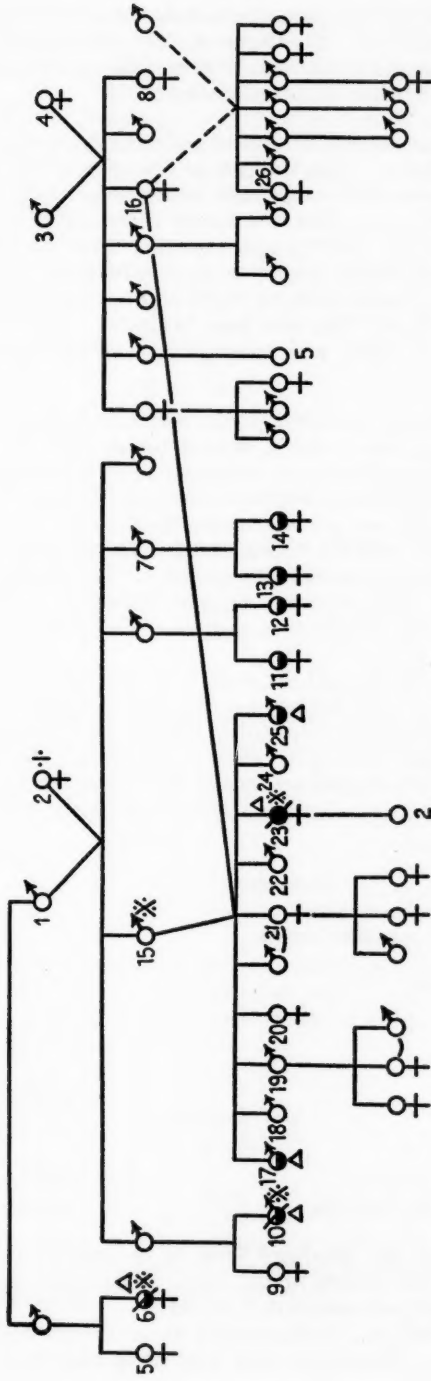
This patient has cerebellar ataxia, nystagmus, retinitis pigmentosa, digital abnormalities, and ptosis. She had a sister who was similarly affected.

*Case VI. Retinitis pigmentosa with partial deaf-mutism.*

Born 1903; admitted 1935.

*Family history.* (See pedigree diagram opposite.)

1—a small, healthy man. 2—died of heart failure; weight 21 st. 3—died aged 62 years. 4—died aged 66 years. 5—healthy. 6—mental defective, deaf, dumb, and blind; said to have been so like the patient that 'one wouldn't know them apart'. 7—died, aged 23 years, of meningitis. 8—died in childhood. 9—normal. 10—eighteen years younger than his sister, imbecile, defective speech, blind when nine, and now dead. 11 and 12—both have very bad sight, the younger being the worse. 13 and 14—both had very bad sight, even at the age of 2 years. 15—the father; died in 1905, aged 44 years, of a strangulated hernia. He was not related to his wife before marriage. He was healthy, but his speech was thick and difficult to understand. 16—the mother; she was said to have suffered from diabetes, but is healthy now; speech and sight normal. She married a second time after her first husband's death, and had seven normal children by this marriage of which the second (26) died in infancy. Three of these children each have a normal child. 17—became deaf after scarlet fever. Night-blind when aged 24 years and has been blind since the age of 36 years. 18—died, aged 5 years, of diphtheria. 19—normal and has three healthy children; the youngest



● Retinitis pigmentosa  
○ Failing sight  
\* Speech defect  
△ Deafness

○ Mental defective  
-I- Obesity  
CASE VI.

two are twins. 20—died, aged 3 years, of measles. 21—healthy and children normal. Twin brother stillborn. 22—Normal. 23—the patient. 24—died, aged 10 months, of meningitis. 25—deaf from infancy, night-blind when aged 32 years and now the sight is deteriorating.

*Past history.* Birth was normal, at first she appeared healthy, but used to scream violently as a baby. She walked at the age of  $2\frac{1}{2}$  years. Her mother says that she learned to speak, and became deaf only after having diphtheria when aged 3 years. She was found at school to be a defective and went to a home after the leaving age. At this time her sight began to fail, but it remained good enough for her to go into domestic service. When 19 years she had an illegitimate stillborn child, and a second in her 23rd year which died after a few days. She was said to have a violent temper. In 1934 she was certified as blind and subsequently admitted to Leavesden Hospital.

*Present condition.* She is feeble-minded, easily upset, and at times has been impulsively violent. She is facile, easy to please, and was co-operative in the investigations. She appreciates attention, likes fancy objects and new clothes. She is an excellent ward worker. She is able to see objects at least six feet in front of her and can get about the ward to work. She is night-blind. The disks are waxy and the vessels small. The pigment is practically confined to a linear distribution in the course of the vessels. The irides are grey-blue in colour. There is no nystagmus. There are no marked stigmata of degeneration; the skeleton is normal. The skin is soft and the hair fine.

The blood-pressure is 135/75, and the pulse 70 to 84. The pupils are equal and react to light. She is deaf, but can hear when one shouts. She lip-reads well. Her speech is limited and indistinct, but she is improving, and with practice one can understand most of her simple sentences. She does not have headaches. She has well-developed secondary sex-characteristics, her breasts are pendulous; she menstruates for five days out of twenty-two.

#### *Investigations:*

##### *Craniometry.*

Distance between inner canthi	.	.	.	3.5 cm.
Mean breadth of palpebral fissures	.	.	.	2.7 cm.
Ear breadth	.	.	.	12.8 cm.
Maximum breadth	.	.	.	14.8 cm.
Breadth index	.	.	.	87
Anterior length	.	.	.	10.7 cm.
Maximum length	.	.	.	19.1 cm.
Length index	.	.	.	56
Cephalic index	.	.	.	78
Height	.	.	.	13.4 cm.
Circumference	.	.	.	55.2 cm.
Capacity—Lee's formula	.	.	.	1419 c.c.
Penrose's formula	.	.	.	1390 c.c.

X-rays of the skull show the pituitary fossa to be small, with what might be some calcification at the mouth of the fossa. The tables and sinuses are normal. The hands and feet were not X-rayed.

Height 62 in. Span  $60\frac{1}{2}$  in. Pubis-vertex 34 in. Pubis-feet 28 in. Her weight was 8 st.  $11\frac{1}{2}$  lb. There has been very little variation since admis-

sion. The temperature, taken four-hourly by the mouth, was 98.8°, 99.6°, 99°, and 99° F. on four evenings out of ten.

A blood-count showed—red cells 4,240,000 per c.mm.; haemoglobin 73 per cent.; colour index 0.86; white cells 13,650 per c.mm.; polymorphs, mature 54.5, immature 15, lymphocytes 23.5, monocytes 5.5, eosinophils 1, basophils 0.5 per cent. No signs of infection were found to account for the leucocytosis.

Serum-calcium 10.3 mg. per 100 c.c., plasma-phosphate 3.5 mg. per 100 c.c., plasma-cholesterol 187 mg. per 100 c.c.

Glucose tolerance curve:

0 hrs.	.	.	112 mg. %
$\frac{1}{2}$ "	.	.	152 "
1 "	.	.	216 "
$1\frac{1}{2}$ "	.	.	228 "
2 "	.	.	158 "

Urine: red-yellow in colour, S.G. 1014, acid reaction, a trace of albumin, but no sugar or phenylpyruvic acid. Some infection, no casts.

Water-salt metabolism: After four days on a constant diet of low chloride content, the following figures were obtained:

	<i>Urine volume.</i>	<i>Sodium chloride.</i>
5th day	1723 c.c.	7.66 gm.
6th "	2258 "	7.56 "
7th "	1644 "	5.51 "
8th "	2170 "	12.8 "
9th "	1755 "	7.9 "

Ten grams of sodium chloride were given on the eighth morning. The chloride excretion was slightly diminished compared with the controls.

Urine dilution test:

<i>Time.</i>	<i>Urine volume.</i>
6.50 a.m.	80 c.c.
8.50 "	350 "
9.55 "	700 "
11.0 "	170 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The rate and volume were normal, but the excretion was delayed.

Melanosome dispersion has been produced by the urine; the blood and cerebrospinal fluid were not tested.

Vitamin C excretion:

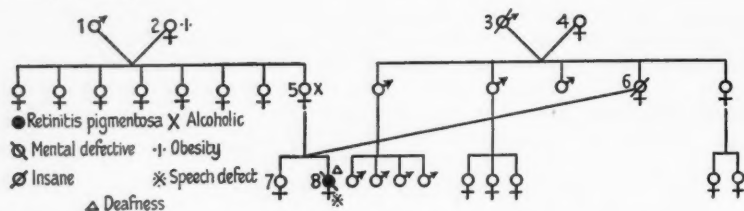
	<i>November 1938.</i>	<i>December 1938.</i>
1st day	19.37 mg.	19.8 mg. ascorbic acid
2nd "	21.2 "	26.83 " "
3rd "	24.36 "	68.29 " "

The second results were after a month's feeding of 50 mg. of ascorbic acid daily. On each occasion 300 mg. of ascorbic acid were given on the third morning. There was no vitamin deficiency.

*Case VII.* Retinitis pigmentosa with deaf-mutism, skeletal abnormalities, and microphthalmos.

Born 1907; admitted 1932.

*Family history.*



1—healthy and intelligent. 2—a stout woman. 3—died in 1903 in a mental hospital; apparently a paraphrenic. 4—a stout woman, died aged 72 years. 5—the father, not related to his wife before marriage; he was healthy and intelligent, but an alcoholic who was unfaithful; he deserted her when the patient was an infant and has not been heard of since. He was one of eight, the siblings were thought to be healthy, but the order of the family is not known. 6—the mother died 1935, aged 56 years; she was in a mental hospital for six years before her death from an empyema. Her sight and hearing were good; she was apparently a paraphrenic. Her siblings were normal and their children healthy. 7—a premature child, born in 1905, who died at 3 months; no skeletal abnormality known. 8—the patient.

*Past history.* Her birth was normal, she was always deaf, made noises when a year old and walked at 2 years. She was thought to be backward from the age of 18 months. She went to a special school and to a hospital for defectives in 1919, where she remained until her transfer to Leavesden Hospital. Her sight was noticed to be failing when she first went to school. When she was 12 years she was quiet, clean, and looked after herself.

*Present condition.* She is an imbecile with a friendly disposition, but is very noisy in efforts to make herself understood. She is rather excitable, has much energy, and is a good worker. She can see a hand waved seven or eight yards from her. She is night-blind, and her visual fields are much contracted. Her disks are waxy, the vessels are very small, and can be traced on the retina only with difficulty. Spidery pigment is much in evidence over the central and peripheral areas. Her eyes are small and rather pig-like. The irides are grey-blue and there is lateral nystagmus. She is thin, her face is deeply wrinkled, the chin is receding, the eyebrows slope downwards and outwards, the superior maxillae are prominent, and the lips are pursed. The lobules of the ears are adherent, and the palate is high but not narrow. Her hands are hard as if she did heavy work, which is not the case, and the skin is deeply and abnormally lined.

The skull has prominent parietal eminences, and there is a deep transverse depression above the occiput. Her neck is extremely long, due to a considerable dropping of her chest; it appears to be over an inch longer than that of another patient of the same height. When the arms are folded in front, the inner borders of the scapulae are vertical instead of tilted in the usual way. The fingers do not show the normal tapering, and the usual bossing of the knuckles is absent. The fourth toes on both feet are short, and they lie in a plane above the rest, on top of the third and fifth toes. The blood-pressure is



120/65, pulse 80 to 94. There is much venous pulsation in the neck, and a functional apical systolic murmur. There are transverse grooves on the teeth. There are calcified glands in the right iliac fossa and the right kidney is easily palpable. There is ptosis and wrinkling of her forehead on looking upwards. The pupils are equal and react to light. She is completely deaf, makes noises, but cannot make herself understood, and has only a small range of sounds. She has not complained of headaches. The hips are like a boy's and the breasts are little formed. The menses were painful and scanty until the last two years when they have become more frequent, and recently they have lasted three days in each three weeks.

*Investigations:*

*Craniometry.*

Distance between inner canthi . . . . .	2.9 cm.
Mean breadth of palpebral fissures . . . . .	2.35 cm.
Ear breadth . . . . .	12.4 cm.
Maximum breadth . . . . .	14.6 cm.
Breadth index . . . . .	85
Anterior length . . . . .	9.1 cm.
Maximum length . . . . .	17.6 cm.
Length index . . . . .	52
Cephalic index . . . . .	83
Height . . . . .	14.4 cm.
Circumference . . . . .	52.7 cm.
Capacity—Lee's formula . . . . .	1391 c.c.
Penrose's formula . . . . .	1220 c.c.

X-rays of the skull show no abnormality. The hands and feet were not X-rayed. X-rays of the cervical vertebrae show that the cause of the apparent elongation of the neck is a severe dropping of the thorax.

Height 60 in. Span 60 in. Pubis-vertex 31 in. Pubis-feet 29 in. Her weight was 6 st. 11 lb., and there has been little variation since admission. The temperature was taken four-hourly by the mouth for ten days. There was hyperthermia of 99° to 99.4° F., the temperature dropping to normal only at nights.

A blood-count showed—red cells 4,510,000 per c.mm.; haemoglobin 89 per cent.; colour index 0.99; white cells 4,750 per c.mm.; polymorphs 55, lymphocytes 35, eosinophils 3.5, monocytes 6.5 per cent.

Serum-calcium 10.2 mg. per 100 c.c., plasma-phosphate 3.66 mg. per 100 c.c., plasma-cholesterol 169 mg. per 100 c.c.

Sedimentation rate = 2 mm. in one hour.

Urine: light yellow, S.G. 1024, acid reaction, no abnormal constituents, no phenylpyruvic acid, some infection.

Water-salt metabolism: After four days' feeding on a constant diet of low chloride content, the following figures were obtained:

	<i>Urine volume.</i>	<i>Sodium chloride.</i>
5th day . . . . .	1124 c.c.	5.17 gm.
6th „ . . . . .	1380 „	5.32 „
7th „ . . . . .	1353 „	3.99 „
8th „ . . . . .	1771 „	11.61 „
9th „ . . . . .	1625 „	8.29 „

Ten grams of sodium chloride were given on the eighth morning. There was no chloride retention.

## Urine dilution test:

Time.	Urine volume.
7.35 a.m.	400 c.c.
8.30 "	550 "
9.50 "	300 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The rate and volume were normal, but there was a delay in secretion.

Melanosome dispersion has been shown by the urine and blood, but not by the cerebrospinal fluid.

## Vitamin C excretion:

	November 1938.	December 1938.
1st day . . .	6.71 mg.	16.23 mg. ascorbic acid
2nd " . . .	11.56 "	18.79 " "
3rd " . . .	16.62 "	26.92 " "

The second results were after a month's feeding on 50 mg. of ascorbic acid daily. On each occasion 300 mg. of ascorbic acid were given on the third morning. There was a vitamin deficiency.

Stools negative for *B. tuberculosis*.

*Case VIII. Retinitis pigmentosa with deaf-mutism.*

Born 1891; admitted 1936.

*Family history.* (See pedigree diagram opposite.)

1—died of tuberculosis; otherwise normal. 2—normal, a sister of the maternal grandmother; she died of tuberculosis. 3—died aged 87 years. She remarried after her first husband's death; nothing is known of either her first or second families. 4—normal. 5—a maternity nurse with a large, normal family. 6—intelligent, but always had severe headaches; hearing and sight normal; died, aged 62 years, of cerebral haemorrhage. 7—died aged 70 years; healthy; sight and hearing normal. 8—illegitimate; normal. 9—cataract said to have developed at school age; sight quite good; an alcoholic who became insane. 10—normal; one child died from diphtheria, the other is well. 11—normal, with five bright children. 12—normal, with six healthy children. 13—stillborn. 14—the patient. 15—stillborn. 16—normal. 17—normal, with twin sons. 18—stillborn.

In addition there were several miscarriages. All the labours are said to have been difficult.

*Past history.* He is said to have been born deaf. He was backward in walking, but was clean and teething was normal. He went to a school for the deaf and dumb when an infant. He was noted as being feeble-minded between the ages of 10 and 12 years, and at this time he began to bump into objects and grope for things which were offered to him. When 15 years he went into a public assistance institution, where he remained for 30 years until admitted to Leavesden Hospital in 1936. He had diphtheria, whooping-cough, and measles when a child.

*Present condition.* He is solitary and dislikes being disturbed. When provoked or annoyed he hits anyone who is near him. He talks to himself a great deal, but one cannot understand what he says. He is usually inaccessible and non-co-operative. His mental age on admission was 8.5 years by performance tests. He is practically blind. It is difficult to ascertain from his reactions whether he has even light perception. The disks are waxy, the retinae atrophic, and the vessels small. Spidery pigment is



sparsely distributed in the equatorial regions. Posterior polar cataracts are present. The pupils are contracted, but dilate up equally with atropine. The irides are grey with some brown speckling. No nystagmus. His appearance is not abnormal. His hair is black and his skin rather dry. Stigmata of degeneration are not marked, and his skeleton is normal. His blood-pressure is 122/75, pulse 70, the heart is normal, but the arteries are thickened and tortuous. The circulation in his extremities is quite good. There is no gross abnormality of the central nervous system, other than complete deafness and inability to express himself. He makes noises. He does not have headaches. The genitalia and sex characteristics appear to be normal.

*Investigations:*

*Craniometry.*

Distance between inner canthi	.	.	.	3.0 cm.
Mean breadth of palpebral fissures	.	.	.	3.0 cm.
Ear breadth	.	.	.	13.5 cm.
Maximum breadth	.	.	.	15.4 cm.
Breadth index	.	.	.	88
Anterior length	.	.	.	11.3 cm.
Maximum length	.	.	.	19.2 cm.
Length index	.	.	.	59
Cephalic index	.	.	.	80
Height	.	.	.	14.0 cm.
Circumference	.	.	.	55.9 cm.
Capacity—Lee's formula	.	.	.	1531 c.c.
Penrose's formula	.	.	.	1460 c.c.

X-ray examination shows the pituitary fossa to be enlarged both in width and depth, its shape being angular rather than curved. The rest of the skull and sinuses appear normal. The hands and feet were not X-rayed.

Height 64 in. Span 66 in. Pubis-vertex  $33\frac{1}{2}$  in. Pubis-feet  $30\frac{1}{2}$  in. His weight was 8 st.  $5\frac{1}{2}$  lb. It varies very little. The temperature was normal when taken by the mouth four-hourly for ten days.

A blood-count showed—red cells 5,010,000 per c.mm.; haemoglobin 103 per cent.; colour index 1.03; white cells 4,600 per c.mm.; polymorphs 48.5, lymphocytes 38.5, monocytes 9, and eosinophils 4 per cent.

Serum-calcium 10.3 mg. per 100 c.c., plasma-phosphate 3.47 mg. per 100 c.c., plasma-cholesterol 184 mg. per 100 c.c.

*Glucose tolerance curve:*

0 hrs.	.	.	68 mg. %
$\frac{1}{2}$ "	.	.	98 "
1 "	.	.	126 "
$1\frac{1}{2}$ "	.	.	86 "
2 "	.	.	66 "

Urine: yellow, S.G. 1028, acid reaction, a trace of albumin, but no other abnormal constituents, no phenylpyruvic acid, occasional leucocyte, no casts, some calcium oxalate crystals.

Water-salt metabolism: after four days' feeding on a constant diet of low chloride content, the following figures were obtained:

	<i>Urine volume.</i>	<i>Sodium chloride.</i>
5th day	670 c.c.	4.72 gm.
6th "	735 "	4.92 "
7th "	836 "	5.45 "
8th "	886 "	3.90 "
9th "	1508 "	10.7 "
10th "	830 "	8.2 "

Ten grams of sodium chloride were given on the ninth morning. There was no chloride retention.

Urine dilution test:

<i>Time.</i>	<i>Urine volume.</i>
7.10 a.m.	140 c.c.
7.45 "	310 "
10.0 "	410 "
11.0 "	170 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The rate, volume, and secretion were normal.

Melanosome dispersion has been shown on several occasions by the urine, but not by the blood at the only time it was tested.

Vitamin C excretion:

1st day . . .	16.05 mg. ascorbic acid
2nd " . . .	12.79 " " "
3rd " . . .	14.67 " " "

300 mg. of ascorbic acid were given on the third morning, then again on the fourth, fifth, and sixth mornings. The urinary volume for the next 24 hours was 910 c.c. and the output of vitamin C 139.2 mg. The three controls excreted 150, 195, and 220 mg. respectively.

*Case IX.* Retinitis pigmentosa with deaf-mutism and a mild degree of arachnodactyly.

Born 1908; admitted 1931.

*Family history.* (See also pedigree diagram on p. 291.)

1, 2, 3, and 4—not deaf or dumb, sight good. 5—died, aged 63 years, of heart failure. 6—died, aged 62 years, of phthisis. 7—very obese; remarried the brother of her dead husband. 8 and 9—double hare-lips, both died aged about 4 months; neither had a cleft palate. 10—the father; a small man, no abnormality. 11—epileptic mental defective. 12—the mother, normal. 13—number not known, but they were normal. 14—insane. 15—hare-lip, but no cleft palate. 16—born 1906; double hare-lip and cleft palate; died aged 6 weeks. 17—born 1907; single hare-lip; palate normal; sight, speech, and hearing good. 18—the patient. 19—born 1910; long hands, feet, fingers, and toes; sight normal; not deaf or dumb. 20—born 1913; deaf-mute, night-blindness 1922; moderate amount of equatorial pigment; waxy disks, vessels fairly small. 21—born 1914; double hare-lip and cleft palate; mental defective. 22—born 1916; insane. 23—born 1920; died of heart failure, aged 16 years. 24—born 1921; deaf-mute; contracted visual fields; recently night-blind; a little peripheral pigment; very thin vessels, and disks small and atrophic. 25—born 1928; normal. 26—two normal children.

*Past history.* Normal birth, walked at the age of 2 years, was clean, and teething was normal. Measles, whooping-cough, chicken-pox, and scarlet fever as a child. He went to a school for the deaf when aged 5 years, for the blind when 9 years, and to a mental hospital when 17 years. He was then reported to be quarrelsome and difficult to manage, and was said to be almost blind, deaf, and unintelligible. He was still able to see well enough in 1931 to understand the signs that were made to him.

*Present condition.* He lies quietly in bed, gives no trouble, and keeps himself clean. He dislikes being disturbed, and may become aggressive at these times. His mental condition appears to be deteriorating. The left pupil is irregular, contracted, and eccentric, and the opening is filled by a dense membrane. There is aphakia (operation for cataract in 1924) and the iris is adherent to the lens capsule. The fundus cannot be seen. In 1935 he was found to have a pale right disk, but there was a posterior cortical cataract. All that is now visible is pigment in the peripheral portions of the retina of typical spider-like form; the cataract is growing very dense. He is still just able to see large objects near to him. He is night-blind. There is heterochromia, the left iris is yellow-brown, the right blue. There is marked divergent strabismus and nasal eccentricity of the right pupil. The skin is dry but not pigmented. The hair is brown. The palate is rather high, and the ears long and narrow. The teeth are normal. There are no signs of a cleft palate or hare-lip. The chest is long and flat, and there is some winging of the scapulae. There is a slight dorsal kyphosis. The forehead is prominent. The limbs are very long and also the fingers, but the length and narrowness is most accentuated in the feet and toes, which approximate to those seen in a true case of arachnodactyly. There is no undue laxity of the ligaments. The heart is not enlarged and there are no murmurs, but the pulmonary second sound is accentuated. His peripheral circulation is good. The blood-pressure is 110/70. There is advanced bilateral tuberculosis of the lungs. The reflexes are brisk. It is reported that each time he blinks his eyes jerk upwards and to the right. He is quite deaf but makes noises. He does not appear to have headaches. His genitalia are normal, and the secondary sex characteristics well marked.

*Investigations:*

*Craniometry.*

Distance between inner canthi . . . . .	3.2 cm.
Mean breadth of palpebral fissures . . . . .	2.6 cm.
Ear breadth . . . . .	12.6 cm.
Maximum breadth . . . . .	14.5 cm.
Breadth index . . . . .	87
Anterior length . . . . .	10.7 cm.
Maximum length . . . . .	18.9 cm.
Length index . . . . .	57
Cephalic index . . . . .	77
Height . . . . .	13.4 cm.
Circumference . . . . .	54.6 cm.
Capacity—Lee's formula . . . . .	1396 c.c.
Penrose's formula . . . . .	1340 c.c.

An X-ray of the skull showed the pituitary fossa to be of normal size. The tables were thin and fused, and the frontal sinus small.

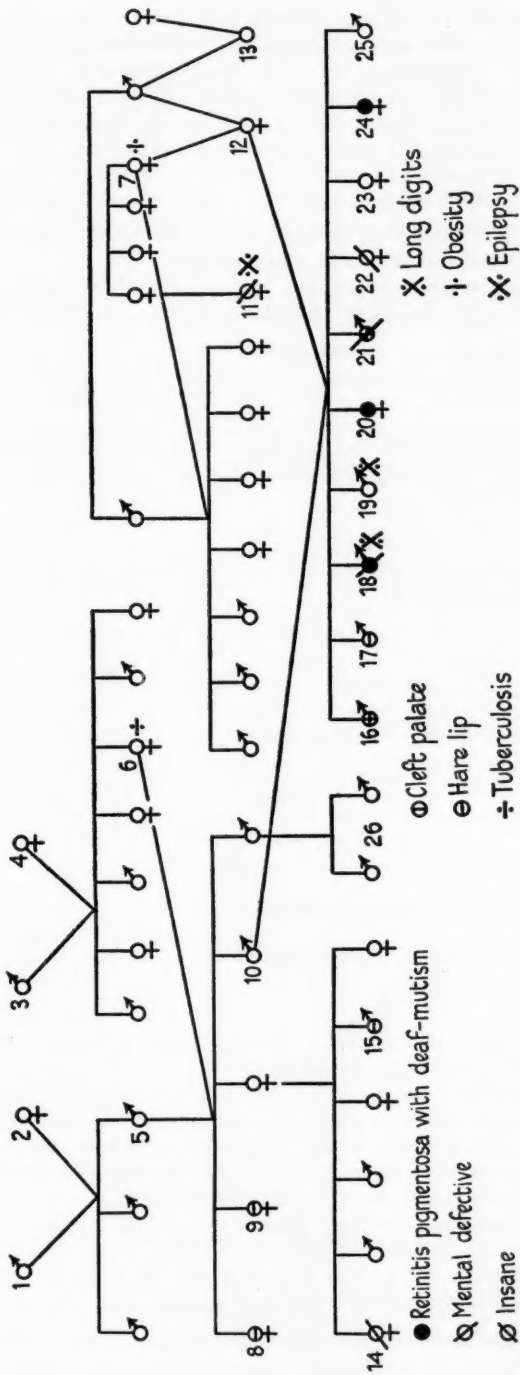
Height 67 in. Span 69 in. Pubis-vertex 32 in. Pubis-feet 35 in. His weight was 8 st. 11 lb. There were occasional elevations of temperature, but in view of his tuberculous state these are not of importance here.

A blood-count showed—red cells 5,230,000 per c.mm.; haemoglobin 91 per cent.; colour index 0.87; white cells 11,000 per c.mm.; polymorphs, mature 57.5, immature 8, lymphocytes 19, eosinophils 14.5, monocytes 1 per cent.

Serum-calcium 10.1 mg. per 100 c.c., plasma-phosphate 4.55 mg. per 100 c.c., plasma-cholesterol 173 mg. per 100 c.c.

Urine: yellowish-red in colour, acid reaction, S.G. 1030, no abnormal constituents, no phenylpyruvic acid, deposit of urates.





CASE IX.

## Urine dilution test :

Time.	Urine volume.
7.10 a.m.	160 c.c.
7.30 "	200 "
8.0 "	330 "
8.30 "	360 "
9.20 "	190 "
10.0 "	160 "
10.50 "	60 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The volume and rate were normal, but the secretion was delayed.

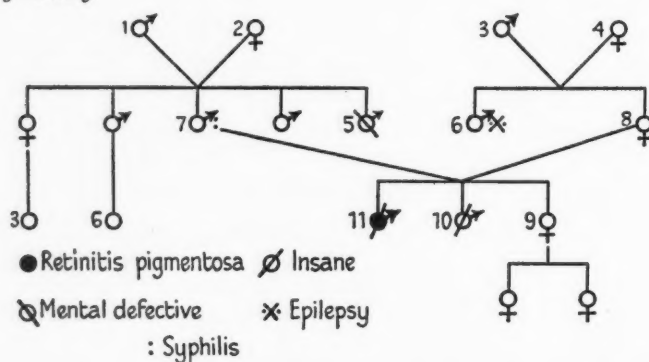
A slight melanosome dispersion has been observed by the urine, but the blood and cerebrospinal fluid gave negative results on a single test.

## Test-meal in 1934 (Ewald's method) :

Free hydrochloric acid .	46 c.c. N/10 NaOH
Total acid .	55 " " "

There was no increase in vitamin C output four hours after giving 300 mg. of ascorbic acid. This was to be expected as there was no supplementary feeding and he was tuberculous.

*Case X.* Retinitis pigmentosa, with schizophrenia and hypogenitalism. Born 1887; admitted 1921.

*Family history.*

1—died, aged 70 years, of paralysis. 2—died aged 80 years. 3—died aged over 80 years. 4—died, aged 70 years, of a stroke. 5—a mental defective, now dead. 6—married, but no children; fell when aged 68 years and had fits afterwards, from which he died. 7—the father; he had syphilis before marriage; died, aged 28 years, from rheumatism and heart failure; his sight was good. 8—the mother, born in 1863; she was not related to the father before marriage; her fundi are normal; no miscarriages. 9—married, with two normal children; has to wear glasses to read at night. 10—failed to keep any job for long, became impulsively violent, was under the influence of auditory hallucinations; he has been in a mental hospital since 1918; he is not obese and his skeleton and fundi are normal. 11—the patient.

*Past history.* His birth was not difficult; he grew up as a bright child and earned his living by selling stationery. Later he became impulsively violent,

as his brother had been, smashed windows, and shut his mother out of the house; he was then certified. He had rheumatism and typhoid fever in his youth, and frequently complained of frontal headaches. On admission he was apathetic, disinterested in his surroundings, impulsive in his actions, and under the influence of auditory hallucinations. He was often wet and dirty. His behaviour improved, but he has never done any work. His mental age was found to be  $7\frac{10}{12}$ , but it is doubtful if this figure is reliable. In 1936 his feet and ankles became swollen and he has taken little exercise since. Owing to his inaccessibility his eyesight had never been noticed to be failing.

*Present condition.* He now sits in a chair all day and does not employ himself in any useful way. He never speaks unless spoken to and then says little. He feeds himself and is clean by virtue of being led to the lavatory at intervals. He is quiet and placid, expresses no delusions, and does not appear to be hallucinated. He appears to have a visual acuity of about 6/12, there seems to be some field limitation, but it is not marked. He has waxy disks and small vessels, much spidery pigment over the equatorial regions best seen on the right side, with marked linear deposits in relation to the veins of the left retina. The irides are grey-blue in colour with some brown speckling medially. There is no nystagmus. He is generally obese due to his inactivity. The fat is not centrally distributed, though the hands are both small and the fingers long and tapering. There is a hammer-deformity of the great toes, and although the remainder are quite long, they are also broad and flat. He has a dorsal kyphosis and protruding lips, but the features are not abnormal. There is no polydactyly. The skin is smooth and the hair grey. The blood-pressure is 155/90, the vessels are normal. There is mitral stenosis, but no signs of failure at rest. The peripheral circulation is poor and there is occasional ulceration of the legs and feet in cold weather. He has a little bronchitis. The central nervous system appears normal. He had frontal headaches for many years but they are less severe now. The genitalia are definitely undersized. The beard is soft and scanty, but the pubic hair is normal. His obesity gives his body a female appearance.

*Investigations :*

*Craniometry.*

Distance between inner canthi . . . . .	3.5 cm.
Mean breadth of palpebral fissures . . . . .	2.75 cm.
Ear breadth . . . . .	14.0 cm.
Maximum breadth . . . . .	14.8 cm.
Breadth index . . . . .	94
Anterior length . . . . .	10.2 cm.
Maximum length . . . . .	19.7 cm.
Length index . . . . .	52
Cephalic index . . . . .	75
Height . . . . .	13.4 cm.
Circumference . . . . .	55.8 cm.
Capacity—Lee's formula . . . . .	1464 c.c.
Penrose's formula . . . . .	1450 c.c.

X-ray examination of the skull shows no abnormality. The hands and feet were not X-rayed.

Height 68 in. Span  $68\frac{1}{2}$  in. Pubis-vertex 32 in. Pubis-feet 36 in. His weight has increased without fluctuation from 10 st. 6 lb. in 1934 to the present weight of 13 st. 6 lb. His temperature, taken four-hourly for ten days by the mouth, was normal.

A blood-count showed—red cells 4,820,000 per c.mm.; haemoglobin 99 per cent.; colour index 1.03; white cells 7,400 per c.mm.; polymorphs 46, lymphocytes 45.5, eosinophils 3.5, monocytes 4, basophils 1 per cent.

Serum-calcium 9.6 mg. per 100 c.c., plasma-phosphate 2.77 mg. per 100 c.c., plasma-cholesterol 190 mg. per 100 c.c.

Urine: yellow, S.G. 1017, acid reaction, no abnormal constituents, no phenylpyruvic acid.

Water-salt metabolism: After four days' feeding on a constant diet of low chloride content, the following figures were obtained:

		Urine volume.	Sodium chloride.
5th day	.	1030 c.c.	6.18 gm.
6th "	.	1027 "	5.34 "
7th "	.	646 "	3.30 "
8th "	.	1212 "	5.60 "
9th "	.	940 "	10.52 "
10th "	.	890 "	8.10 "

Ten grams of sodium chloride were given on the ninth morning. The volume secreted after the chloride was given is diminished instead of increased. There is no chloride retention.

Urine dilution test:

Time.	Urine volume.
6.55 a.m.	240 c.c.
7.30 "	410 "
8.15 "	260 "
9.2 "	130 "
9.50 "	120 "
10.58 "	100 "

1,000 c.c. of water were given between 6 and 6.30 a.m. The volume and rate of secretion were normal.

Melanosome dispersion by the urine and blood has been observed. The cerebrospinal fluid was not tested.

Vitamin C excretion:

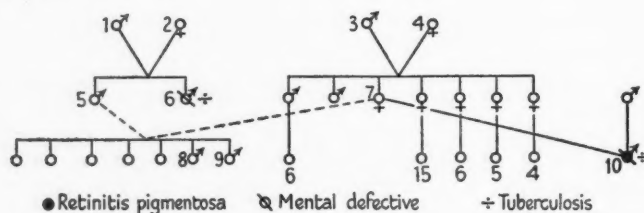
1st day	.	11.55 mg. ascorbic acid
2nd "	.	15.37 "
3rd "	.	17.36 " " "

300 mg. of ascorbic acid were given on the third, fourth, fifth, and sixth mornings. In the next twenty-four hours he passed 1,390 c.c. of urine and excreted 140.3 mg. of vitamin C. The three controls excreted 150, 195, and 220 mg. respectively.

*Case XI. Retinitis pigmentosa with pes cavus.*

Born 1913; admitted 3.5.1938; died 8.11.1938.

*Family history.*



1—died of gout. 2—died of bronchitis. 3 and 4—alive and well; not related before marriage. 5—the mother's husband. 6—a mental defective, who died from phthisis. 7—the mother, who has normal fundi; none of her 36 nieces and nephews have any skeletal abnormality or anything wrong with their eyes; her siblings are normal. 8—normal. 9—myopic, but not night-blind. 10—the patient, thought to have been illegitimate by a father who is not known. 8, 9, and 10—were born by Caesarian section, as the mother had previously had four stillborn children and one which died from convulsions. She has a contracted pelvis.

*Past history.* Born at full term by Caesarian section. Had whooping cough, scarlet fever, and pneumonia as a child. The step-father left the mother and the patient was sent into a hospital for defective children as he was easily led, stole, and could not be controlled. His mother had found him to be night-blind in his early teens, and he was very clumsy, probably owing to a field defect. When he was found to be tuberculous he was transferred to Leavesden Hospital.

*Condition on admission.* He had a mental age of  $8\frac{3}{12}$ , but his memory was defective. His behaviour was good, but he did not employ himself usefully. He was able to see fairly well by day, and was slightly myopic. He was night-blind and had some definite contraction of his visual fields. His fundi showed waxy disks, small vessels, and a fair amount of equatorial and peripheral spidery pigment. The irides were grey. No heterochromia was recorded. His chest was long and there was a marked Harrison's sulcus present with some beading. The legs and arms were long and thin, and there was well-marked bilateral pes cavus. The heart was not enlarged. Pulmonary second sound accentuated, reduplicated apical second sound. Soft systolic murmur not conducted outwards. Signs of pulmonary tuberculosis particularly marked at the right apex. The tongue was red and sore, and there were calcified glands in the right iliac fossa. The nervous system was normal and there was no record of epilepsy or headaches. The genitalia were normal.

#### *Investigations:*

##### *Craniometry.*

Maximum length	.	.	.	.	.	17.1 cm.
Maximum breadth	.	.	.	.	.	13.7 cm.
Circumference	.	.	.	.	.	52.1 cm.
Cephalic index	.	.	.	.	.	80

He was not X-rayed, but the pituitary fossa was found to be enlarged on post-mortem examination.

Height 63 in. Pubis-vertex 30 in. Pubis-feet 33 in. His weight was 6 st. 10 lb.

A blood-count showed—red cells 4,730,000 per c.mm.; haemoglobin 90 per cent.; colour index 0.95; white cells 10,650 per c.mm.; polymorphs, mature 63, immature 12, lymphocytes 22, monocytes 3 per cent.

Urine: S.G. 1008, acid reaction, no abnormal constituents, negative for phenylpyruvic acid.

He developed tuberculous enteritis and died six months after admission. An autopsy was made, but the brain has not yet been examined.

Böck and Risak (1934) described retinitis pigmentosa, spastic pes cavus, mental deficiency, gigantism, and an osteoma of the parietal bone in a patient with a clear family history.

This patient had retinitis pigmentosa, pes cavus, mental deficiency, and long lower limbs. His family history was also clear.

*Summary of the Investigations*

(The Roman numerals in the pages following refer to the cases which have been described.)

*Family histories.* In the 10 family histories of the cases with retinitis pigmentosa, 385 relatives have been traced. Of these five had a progressive loss of vision, four became blind at an early age, and three have been verified as cases of retinitis pigmentosa. Seven were mental defectives and nine were insane, figures which are certainly not higher than would be expected in the pedigrees of an equal number of cases of oligophrenia. There were eight with deafness, deaf-mutism, or speech defect, six with cleft palates or hare-lips (all in family IX), six alcoholics, three with gross obesity, two epileptics, two with frequent headaches, one with colour-blindness, and one with congenital cataract. There were five cases of tuberculosis and one of syphilis. Twelve stillborn children are noted. A recessive transmission is suggested by those histories in which sufficient data are available for investigation.

The family history of IV shows a poor stock, but the parents can no longer be traced to render it more complete. It was one of the only two in which consanguinity was found. Of the 11 members traced only one, besides the father and mother, was normal. There were three alcoholics, two cases of insanity, and the patient with retinitis pigmentosa. Stockhard's (1913) work on the production of eye lesions in the offspring of alcoholized guinea-pigs is interesting in this connexion. Case V and a sister with almost identical abnormalities were the product of an alcoholic father who was colour-blind and a mother with deafness and headaches. The history of IX is particularly interesting. In the third generation there are two cases of double hare-lip without cleft palates, and one mental defective. In the 16 members of the fourth there are two with single hare-lips and two with double hare-lips and cleft palates. Three are mental defectives, one is insane, and three are deaf-mutes with retinitis pigmentosa. Moreover, two members of this generation (the patient is one of these) have long limbs and long digits, but no facial deformity. This would seem to be evidence in favour of the relationship between arachnodactyly and status dysraphicus (Pino, Cooper, and Van Wien, 1937).

*General.* The stigmata of degeneration are no more marked than would be expected in these cases. The skin of the hands of case VII is hard, and case III is very freckled. The blood-pressures are mostly normal. There is no more cyanosis in the extremities than is usually seen in defectives, and there are no signs of congenital heart disease. There is no abnormal variation between the summer and winter weights, and sweating, with a single exception (IV), is not marked. This patient has abnormal teeth. No developmental abnormalities have been found in either the respiratory or alimentary



systems. The thyroid glands are normal. Ptosis is present in three cases (III, V, VII). One of these (V) has marked cerebellar signs. One (I) has head-nodding. Four of the obese patients (II, III, IV, X) complain of headaches, referred in three to the frontal region. Three (VII, VIII, IX) are stone-deaf, make noises, but cannot be understood; one (VI) is very deaf, but her speech is to some extent intelligible to those who know her; and a fifth (IV) is slightly deaf, but without speech defect. The sleep rhythms are not disturbed. None have had fits.

*Mental.* There is nothing remarkable about the mental state of these patients. On the whole, the obese patients are placid and the deaf patients unreliable.

*Eyes.* The fundi are typical of retinitis pigmentosa, with a single exception (VI) where the pigment is practically confined to linear deposits along the vessels. In most cases the condition is advanced. The age of onset, when it can be traced, was at 3, 4, 5, 9, 11, 12, 14, 31, and 47 years. In five cases blindness occurred at 39, 40, 47, 54, and 55 years. Cataracts are present in five patients and nystagmus in four. One (IV) has a convergent squint, another (IX) a divergent strabismus and corectopia. If it should be a coincidence, it is remarkable that every case, with the exception of the one (IX) with heterochromia, has grey or blue-grey irides. None have any gross errors of accommodation. In most of the patients the visual fields cannot be measured, but night-blindness has been found in each patient on whom tests could be made.

*Skeleton.* The skeletal measurements show three (IV, V, VIII) of the 11 patients to be well proportioned. Cases I and VI have long trunks and short legs, and one (III) has a long trunk, short arms, and short legs. A case (II) of the Laurence-Moon-Biedl syndrome shows some acromegalic features, but the great degree of kyphosis makes any deductions drawn from the measurements unreliable. Two (II, V) have a kyphoscoliosis, a third (X) a kyphosis, a fourth (IX) a kyphosis, a long chest, and some scapular winging, and a fifth (VII) a dropped chest. In only three of the patients (IV, VI, VIII) are the hands and feet normal; the abnormalities of the digits of the remainder are varied, and concerned with length, breadth, relative size and position, shape, fusion, and number. Of particular interest is the case (XI) with pes cavus and that (IX) with some degree of arachnodactyly. Abnormalities of the digits have been described in the Laurence-Moon-Biedl syndrome (Paton, 1936; van Bogaert and van Lint, 1934; Pesmé and Hirtz, 1937; Mutch, 1937).

An analysis of the cranial measurements shows four of the heads to be small, though only one (III) is less than 20 in. in circumference, and its height is in proportion to the length and breadth. The other three are inclined to be tall, as is the case in most small heads, but the heights of two others (VIII, IX) are rather more than one would expect. Two heads (III, VI) are mildly brachycephalic, and another (II) is slightly dolichocephalic. There are no indications of hydrocephalus as judged by low length and

breadth indices, a high cephalic index, and a height out of proportion to the other measurements. The inner canthus distances are normal, but the palpebral breadths are mostly smaller than the average of 2.75 cm. found for 100 other defectives with head circumferences of more than 20 in. without hydrocephalus. X-ray examination of the skulls of 10 of the patients showed two to have enlarged pituitary fossae, whilst the one who died also had a definite enlargement seen at the autopsy. On the other hand, one fossa (VI) is definitely small. Tracings of the pituitary fossae are shown in

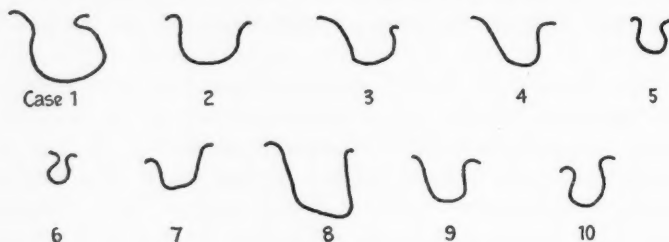


FIG. 1.

Fig. 1. Three of the patients (III, V, IX) appeared to have thin skulls and small sinuses representing the hypopituitary type.

*Obesity.* Four of the cases (I, II, III, IV) have obesity with a central fat distribution, and the inert schizophrenic (X) is generally obese. It is interesting that the blood-cholesterol is raised in each of the first four patients to 203, 245, 208, and 216 mg. per 100 c.c. respectively, whilst its value in the remaining patients is normal.

*Hypogenitalism.* This is present in five of the patients (I, III, V, VII, X), and one (VI) has had two children, of which one was stillborn and the other died soon after birth.

*Hyperthermia.* Three of the patients (IV, V, VII) have a constant mild hyperthermia, measured by the mouth, without any signs of pulmonary tuberculosis or other disease.

*Sugar tolerance.* Three cases (I, II, VI) show a diminished glucose tolerance; two of these have polyuria and one a constant glycosuria, but none have excreted any acetone bodies. The shape of the curve given by VIII suggests an increased glucose tolerance. The curves of the remainder are normal.

*Blood.* The only noteworthy observation in the blood-counts is a lymphocytosis. The percentages of lymphocytes are 46, 31, 65.5, 29, 32.5, 23.5, 35, 38.5, 19, 45.5, and 22, the lowest proportions being unexpectedly found in the tuberculous patients (IX and XI). The serum-calcium and plasma-phosphorus values are normal in each case, and the Wassermann and Meinicke reactions are all negative.

*Other tests.* The routine examinations of the urine and cerebrospinal fluid show no abnormalities of importance. Fractional test meals, with the

exception of case III, mostly show an achlorhydria which was probably reflex in origin, as nasal tubes had to be used to collect the fluid. Histamine was not given.

*Water-salt metabolism.* Both the sodium chloride excretion test and the urine dilution test were controlled against a larger number of patients

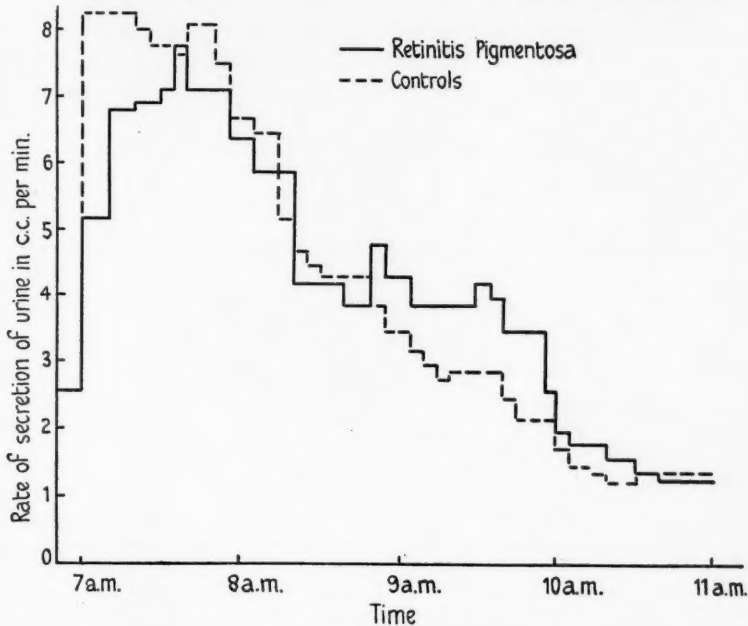


FIG. 2.

without corresponding abnormalities, though all were defectives, and mainly imbeciles.

In the dilution test the average rates of excretion during the test were calculated by dividing the volume of each specimen by the time which had elapsed since the last specimen was passed. A 'normal' graph was made by combining the 12 control curves. This was done by summing the average rates of secretion at each time that a specimen of urine was passed by any of the patients, and averaging the results. The curve given by any one of the patients with retinitis pigmentosa could then be compared with the 'normal' graph. In six cases there was a delay in reaching the maximum rate of urinary secretion and in returning to the resting value. The average rates of secretion for the patients with retinitis pigmentosa are shown in Fig. 2 compared with the 'normal' curve. In every case more than 900 c.c. of urine were passed in the four hours following the water intake, and the average urinary excretion was almost identical with that of the controls.

In the excretion test the average daily output of sodium chloride was

calculated before the salt was given, then the daily difference was found for the two days following, so giving the extra chloride eliminated. In all the cases with retinitis pigmentosa the output was normal compared with the controls, none showing the retention observed in some of Zondek's (1933) cases. The volume 'kick', that is, an increased secretion of urine in the two days following the administration of the chloride, was observed in all the cases except one (X), and was no less than was seen in the controls.

The patient II is not included in these results in view of her age, albuminuria, and arteriosclerosis. Case XI was not investigated, nor was the salt excretion in case IX.

*Melanosome dispersion.* This was observed by the urine of nine of the patients at one time or another; for one it was tested twice with negative results. The blood has produced a dispersion in six of the seven patients examined. Specimens of cerebrospinal fluid in the four tested gave negative results.

*Loewi's eye test.* Two patients (I, III) gave a positive Loewi's eye test. The diastatic index in these cases was 10 and 28.5 units respectively.

*Vitamin C excretion.* Estimations of the urinary vitamin C output were made on six of the female cases, two of the male cases, and nine controls. The output of the females was measured on three successive days, 300 mg. of ascorbic acid being given on the third morning. Both the patients with retinitis pigmentosa and the controls showed a vitamin deficiency. Accordingly 50 mg. of ascorbic acid were given daily to each for a month and the estimations repeated. Four of the six patients with retinitis pigmentosa and two of the six controls still showed a vitamin deficiency.

The male patients were given 50 mg. of ascorbic acid each day for a month before similar estimations were made. Both the experimental cases and the controls still showed a vitamin deficiency. After having 300 mg. on the next three mornings the control cases excreted over 30 per cent. more vitamin C than did the retinitis pigmentosa cases in the next twenty-four hours.

Thus six of the eight patients with retinitis pigmentosa compared with three of nine controls showed a vitamin C deficiency after supplementary feeding, though all had been having similar food for some years.

The estimations were made within five minutes of the time when each specimen of urine was passed, and thus acetic acid was not added as a preservative (Harris and Ray, 1935). Case II is not included in these results as there is a vitamin C deficiency in old age usually in the neighbourhood of 2,000 mg. of ascorbic acid (Gander and Niederberger, 1936). For a similar reason the vitamin C excretions of the tuberculous patients (IX, XI) were not investigated (Abbasy, Harris, and Ellman, 1937; Hasselbach, 1936).

It was not possible to measure the basal metabolic rate, the specific dynamic action of protein, or the blood-bromide in any of these cases.

*Discussion*

The pathological basis of retinitis pigmentosa is now believed to be a heredo-degeneration of the nervous elements of the retina. The blood-vessels have been implicated by a number of ophthalmologists who viewed the condition as primarily choroidal, but the work on which this theory was founded has not been confirmed (Nicholls, 1938; Bourne, Campbell, and Tansley, 1938).

The most adequate explanation of the occurrence of abnormalities in association with retinitis pigmentosa has been given by Panse (1937). The Laurence-Moon-Biedl syndrome is chosen as his example in attempting to explain a variety of disturbances as the result of a single hereditary process. He regards the diencephalon first as an organizer and later as an organ, in the production of the manifestations of this syndrome. He believes that the pathological gene must come into action in the rudimentary diencephalon at a very early stage of development, before the division of the extremities into five digits is fixed. Special importance is attached to the possibility of this explanation of the polydactyly in particular, firstly because the other partial signs of the syndrome point to the diencephalon as the point of origin, and secondly because on this basis a relationship to other disturbances of growth arising from the same focus might be demonstrated. He points out that the conclusions cannot be more than a working hypothesis owing to the present lack of histological verification, but he expresses the view that anatomically detectable maldevelopment in the diencephalon is not an essential condition in the production of the hereditary syndromes arising solely from this regulating organ. A centre of organization may produce its effect without being materially visible, just as in experiments on developmental physiology the organizers have always been observed only by their function. At the same time he puts forward the supposition that in this particular syndrome it is to be expected that the diencephalon as an organ will show signs of maldevelopment. This hypothesis may perhaps be extended to include every case of retinitis pigmentosa. A consideration of pigmentary degeneration of the retina leads one to separate the associated abnormalities into two groups, the first comprising the Laurence-Moon-Biedl syndrome and its variations, the second embracing deaf-mutism.

The conditions which form the first group might be considered as the physical expressions of varying degrees of degeneration involving the regions developed in common with the optic vesicles. On this basis an explanation may be found not only for the Laurence-Moon-Biedl syndrome, but for its partial components, allied conditions, and even apparently simple cases of retinitis pigmentosa. It is supposed that most of these simple cases would show some signs of diencephalic disturbance if they were further investigated. For instance, a melanosome-dispersing substance in the blood and urine, a thyrotrophic substance in the urine, and an abnormal water-salt metabolism have been demonstrated in such patients.



The second group might conceivably be the result of a heredo-degeneration involving the retina and other apparatus of sensory reception. Deafness and deaf-mutism are frequently found in common with retinitis pigmentosa, and Schupfer (1937) has found associated anosmia. Usher (1914) tested the sense of smell of eight of his patients with pigmentary retinal degeneration (of whom two were partially deaf, but without speech defect) and, employing strong odours, found it to be normal for each. In another patient with defective speech and hearing, the senses of smell and taste were normal, but in one whom he did not see himself there was deafness and anosmia. It would be interesting from this point of view to know whether taste had been tested in other cases. Methods for testing partial loss of these senses would be necessary to check the hypothesis. Such tests were not possible on the patients described here. It is obvious that the two groups are not mutually exclusive and the discovery of certain common factors is in no way incompatible with the hypothesis.

The investigations on this series of patients were planned to demonstrate any diencephalic disturbances which might be associated with retinitis pigmentosa, that they might give support to the above supposition. No attempt is made to show that pigmentary retinal degeneration is due to some specific hypophyso-hypothalamic lesion.

In the following discussion of the individual abnormalities, which are mostly described for the first time in this study, the relationship to diencephalic disturbance is briefly indicated. The pars intermedia of the pituitary gland secretes a hormone which will 'expand' the melanophores of the frog and the pigment cells of certain fish. Its presence in solution is easily recognized by injecting it into the dorsal lymph sac of the frog when there is a marked darkening of the animal's skin. The urine at the beginning of the menstrual period, in cases of pituitary disease, pregnancy, hyperthyroidism, migraine, and some cases of cutaneous pigmentation, has been shown to contain a melanosome-dispersing substance (Collin and Drouet, 1933; Jones, 1938). It has not been shown to be present in any tissues of the body except the pituitary gland, and it cannot be demonstrated in the urine of normal persons by this method. Thus it appears to be found in the urine only in pathological conditions of the pituitary body or at periods in which the gland is subjected to physiological stress, and it seems probable that the substance producing these effects is the pituitary hormone.

In consequence some interest is attached to the recent discovery that the blood and urine of cases of retinitis pigmentosa will produce melanosome-dispersion in the frog. This reaction may, moreover, be of use in the differentiation of retinal conditions which are usually regarded as being related to pigmentary retinal degeneration. Thus in a case of gyrate atrophy of the choroid and retina a single specimen of blood and several samples of urine failed to change the colour of frogs. Riddell (1939) could not produce melanophore expansion with the urine of a case of choroideremia, but confirmed the writer's observations by finding that a specimen of urine from four out of five



patients with retinitis pigmentosa darkened the skin of frogs. On the other hand, de Grósz (1939) could not repeat the results on four uncomplicated cases of pigmentary retinal degeneration and suggested that his patients had no accompanying diencephalic disturbances. Mecca (1936) found three of his cases to have migraine, which is one of the conditions in which the urine produces a melanophore expansion. Four of the obese patients described in this paper had headaches, and Zondek (1935) records the frequent occurrence of headache in cases of water-salt obesity. It may be that there is some relationship between these observations.

The obesity observed in four cases had a distribution of the hypothalamic type (Riddoch, 1938), but its characteristics do not conform completely with either the adiposogenital or water-salt varieties described by Zondek (1935). The raised blood-cholesterol in association with this type of obesity has not been previously described, and in the only parallel case discovered in which the cholesterol was measured (Casini, 1937) the value was only 80 mg. per 100 c.c.

The hyperthermia in three cases is interesting. Stewart has under his care two of three brothers who represent a syndrome intermediate between that of Kapuscinski (1934) and the Laurence-Moon-Biedl syndrome<sup>3</sup> who both show a constant hyperthermia which appears to be accentuated by emotional disturbance. Zondek (1935) describes disturbance of thermal regulation as a characteristic sign in water-salt obesity, and describes three cases with prolonged mild hyperthermia. Riddoch (1938) has seen slight or moderate fever in intraventricular gliomas, suprasellar cysts, and tumours in the region of the third ventricle, whilst experimental work confirms the presence of a thermal centre in the hypothalamus.

Three of these cases of retinitis pigmentosa have a diminished glucose tolerance progressing very slowly in severity and without acetone bodies in the urine. The evidence required to attribute a diminished glucose tolerance to the hypothalamus is not clearly defined and there are discrepancies in the criteria of different writers. Lhermitte (1934) quotes two cases of diencephalic glycosuria associated with chloride retention in the tissues, and Zondek (1935) has seen it with hypothalamic obesity. It has also been found in the Laurence-Moon-Biedl syndrome (de Schweinitz, 1923). The hypogenitalism in five of these cases of retinitis pigmentosa may well be an expression of hypothalamic disturbance when considered in conjunction with the other evidence (Berblinger, 1931).

None of the patients showed an abnormal chloride excretion, although this has been found by Zondek (1935) in uncomplicated cases of retinitis pigmentosa. On the other hand, nearly all the cases exhibited a retardation of water

<sup>3</sup> Kapuscinski (1934) found three of the four surviving members of a family to have Friedreich's ataxia, hypogenitalism, mental deficiency, and choroidal sclerosis with myopia. Stewart's cases have Friedreich's ataxia, hypogenitalism, mental deficiency, retinal abnormalities, and obesity, and one has polydactyly. The retinal abnormalities in these patients consist of thread-like vessels in the one and white stippling about the maculae in the other.

excretion compared with the controls, as seen by the results of the urine dilution test. This delay was seen by Wolff (1938) to a very marked degree in two cases of the Laurence-Moon-Biedl syndrome. The abnormality of water secretion is unlikely to be an expression of a defective renal secretion or a prerenal azotaemia (Fishberg, 1939), but there appears to be a renal and an extrarenal factor involved in the action of the hypophyso-hypothalamic system on water and salt metabolism (Boon, 1938). The experiments of Lewy and Gassmann (1937) indicate not only that salt metabolism underlies water output, but also that water excretion is influenced by the hypothalamus.

It is interesting from the point of view of Panse's (1937) hypothesis that in nearly all these cases bilateral abnormalities were found in the limbs, although the digits were sometimes asymmetrical. It may perhaps be that the skeletal maldevelopments represent a form of disturbance less obvious than, but similar to, the polydactyly of the Laurence-Moon-Biedl syndrome. In this connexion the occurrence of a mild degree of arachnodactyly (*dolichosténomélie*) in one of the patients is of interest. This abnormality has been described about as frequently as the Laurence-Moon-Biedl syndrome, though it is probably commoner even in its fully developed form, whilst cases such as the one mentioned here must frequently be seen (Clément, 1939). Nevertheless, pigmentary retinal degeneration has been reported in conjunction with arachnodactyly only on one previous occasion (Stewart, 1939), although it has been seen with a macular coloboma, whilst in a patient at Leavesden Hospital it is associated with cerebro-retinal degeneration. In most cases an associated dislocation of the lens is present, though it is not essential for the diagnosis of arachnodactyly (Marfan, 1938), and it was not found in Stewart's (1939) case, in that with cerebro-retinal degeneration, or in the one described here. Usher (1914) mentions ectopia lentis in three cases with retinitis pigmentosa, and Derigs (1882) found corectopia and ectopia lentis in one case, but neither mentions the extremities. An analogy may be drawn between the disturbance of the rate of growth of the long bones relative to the trunk in arachnodactyly associated with an ocular abnormality and these cases of retinitis pigmentosa with skeletal malformations.

Sladden (1913) grouped the cases showing Loewi's eye sign into two main groups. In the one there was increased activity of the sympathetic system, in the other a disturbed equilibrium of the internal secretions of the body in the direction of a preponderance of the chromaffin system. Loewi (1908) originally demonstrated the sign in some diabetics, and it has also been found in lesions of the stomach. This would probably account for the positive findings in two cases of this series, for one had an increased glucose tolerance and the other symptoms of pyloric obstruction. Nevertheless it is possible that hypothalamic abnormalities explain both the disturbed sugar metabolism and the stomach lesion, for both patients are examples of the Laurence-Moon-Biedl syndrome.

The lymphocytosis which has been found in a number of these patients is

not easily explained. A leucocytosis has been described with hypothalamic disturbances, but Jores and Nothmann (1937) have found a lymphocytosis and eosinophilia in pituitary disease. Dible (1940) found a lymphocytosis in cases of night-blindness, which was of a similar degree to that found in these investigations.

The vitamin C estimations on these patients were made as the result of some experimental work by Sorsby (1938). A German preparation 'Septojod' had caused blindness in some cases when it was used as an intravenous anti-septic. The retinal lesions appeared to be identical with retinitis pigmentosa, and the constituent which caused them was found to be sodium iodate. Sorsby (1938) produced experimental pigmentary retinal degeneration in rabbits both by the use of this drug and other oxidizing agents. He considered that the lesions might perhaps be due to an oxido-reduction system set up in the retina between the vitamin C, which was already present (Bracci-Torsi, 1935), and the oxidizing agent, which was injected. On the other hand, the accumulation of a preliminary reserve of ascorbic acid did not seem to render the animals immune to the action of sodium iodate. It seemed possible that retinitis pigmentosa might be due to some analogous chemical action which would continually destroy the vitamin and so deplete the body reserves. For instance, Cavallacci (1935) showed that the vitamin C content of the retina was reduced by ultra-violet irradiation, as the result of an oxidizing process being accelerated by these rays. The results recorded in the present paper do not allow of any definite conclusions to be drawn, though they are sufficiently suggestive to warrant further investigations. Although the total vitamin C excretion of the patients with retinitis pigmentosa was considerably less than that of the controls, there were exceptions even in the small number of cases examined.

#### *Summary*

1. Eleven cases of retinitis pigmentosa have been investigated.
2. Skeletal abnormality and deformity, melanosome-dispersion in the frog by specimens of blood and urine, headache, hyperthermia, hypogenitalism, hypercholesterolaemia associated with obesity, diminished glucose tolerance, disturbances of the water-salt metabolism, lymphocytosis, and diminished vitamin C excretion are amongst the abnormalities found which are common to several cases.
3. The results are discussed and an attempt is made to interpret them on the basis of a varying degree of degeneration in the nervous system.

I should like to express my thanks to those who have given me so much kind help, in particular Dr. R. M. Stewart, Mr. Arnold Sorsby, Dr. L. S. Penrose, Mr. A. Harold Levy, and the laboratory and nursing staff at Leavesden Hospital.

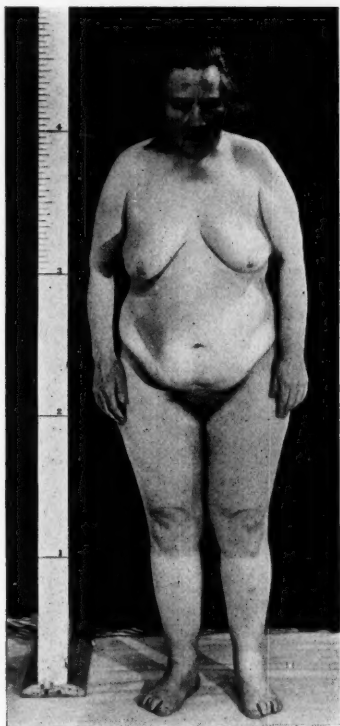
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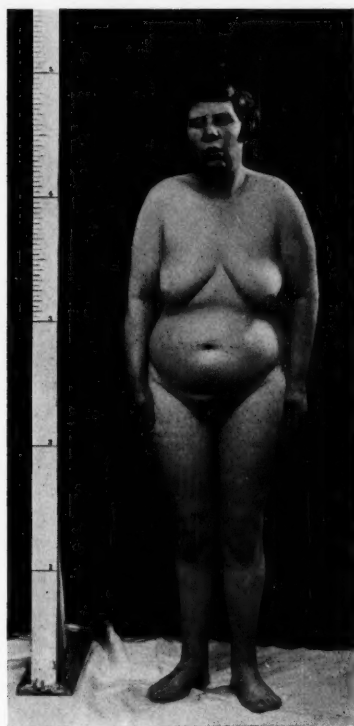
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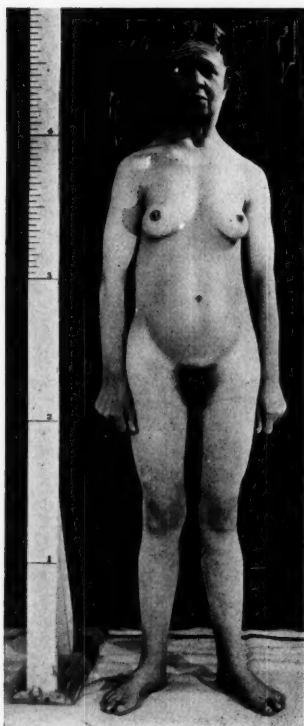




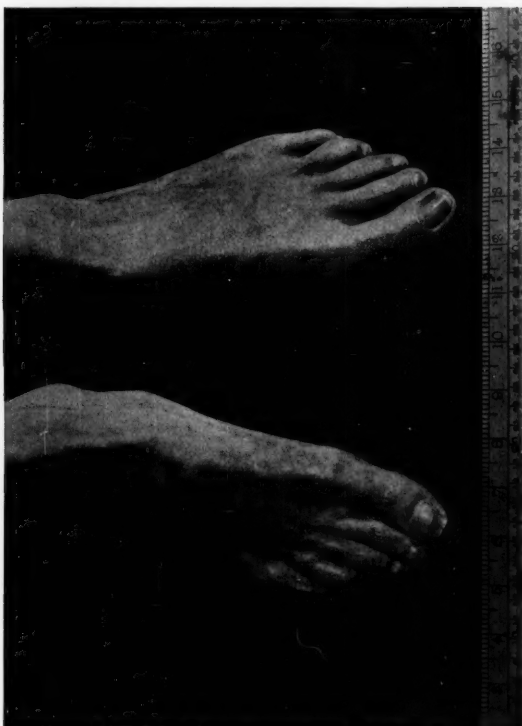
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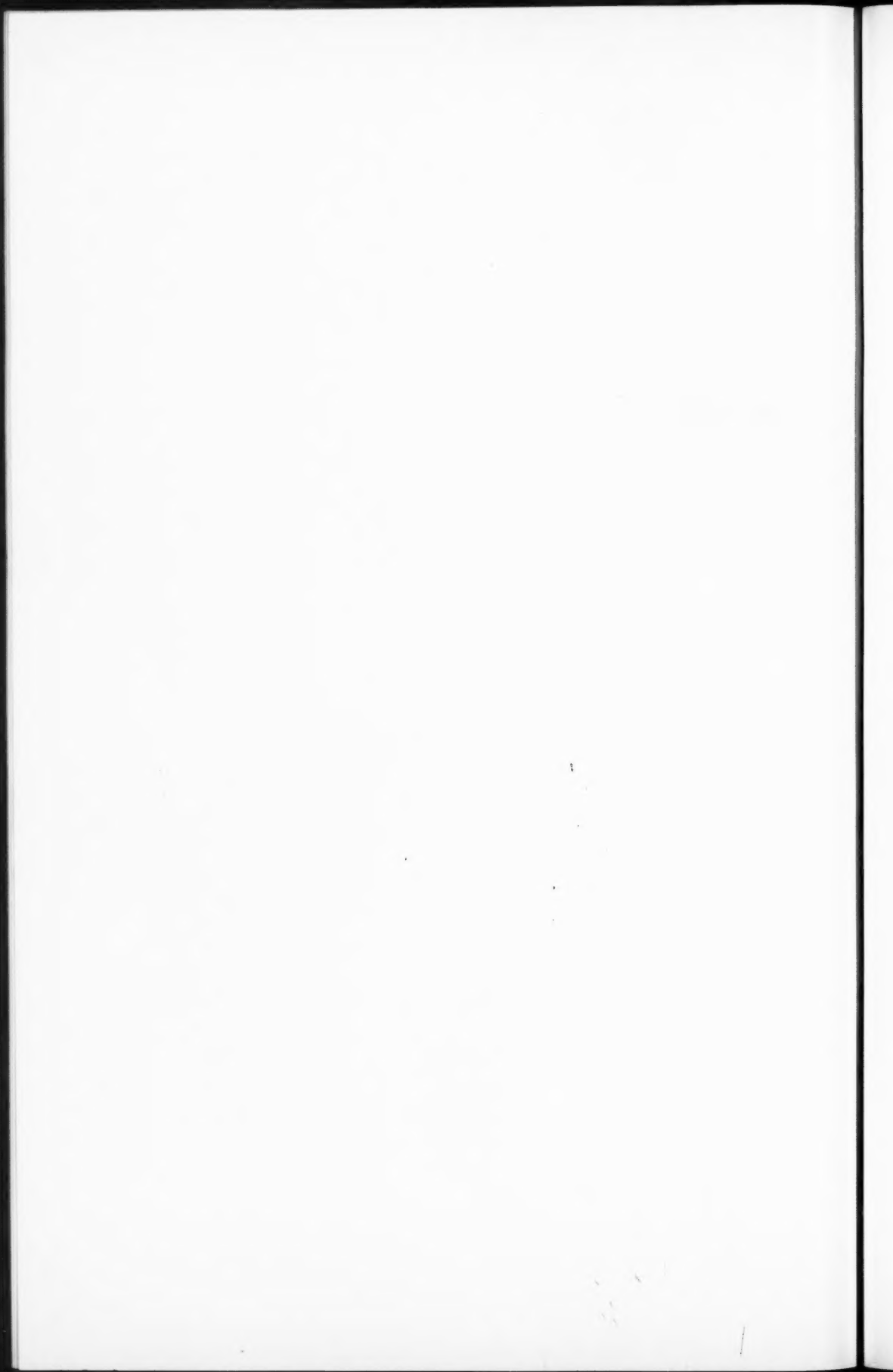
Case IV



Case VII



Case IX



## PREPARATIONS OF TESTOSTERONE IN EUNUCHISM AND HYPOGONADISM<sup>1</sup>

By ALLAN WILLIAM SPENCE

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With Plate 17

SINCE testosterone, considered to be the natural hormone of the testes, was prepared synthetically from cholesterol by Ruzicka and Wettstein (1935) and by Butenandt and Hanisch (1935), numerous investigators have reported strikingly beneficial effects with its compounds in patients with deficient testicular function. As it has a very low potency when given by mouth, and by injection is absorbed so rapidly that frequent injections are necessary, methods of administration aim at increasing its effectiveness by delaying its absorption. Miescher, Wettstein, and Tschopp (1936) showed that, by analogy with oestrone, increased duration and intensity of action are obtained with the aliphatic esters of testosterone, and that the optimum effect is given by the propionate, due, as Deanesly and Parkes (1937) have demonstrated, to slow absorption from the site of injection. Absorption of testosterone is also delayed by implanting it subcutaneously as a compressed tablet, by which means free testosterone becomes as effective as an oily solution of the propionate (Deanesly and Parkes, 1937). It has also been shown that androgens, in common with oestrogens, are absorbed by inunction through the skin (Deanesly and Parkes, 1937; Moore, Lamar, and Beck, 1938), and Foss (1938) has reported the effectiveness of this method of administration in man. That oral therapy may be possible in the future is suggested by the demonstration of Miescher and Tschopp (1938) that methyl testosterone is considerably more active by mouth than any androgens so far tested, as judged by its effect on the prostate and seminal vesicles of castrated rats. Foss (1939b) has indeed produced with this compound full potency in a eunuch and hastened puberty in two boys with hypogonadism. In the present paper are reported the results obtained by these different methods of treatment in two eunuchs and in four patients with hypogonadism; in all potency was established and the development of secondary sexual characteristics induced.

### *Case Reports*

#### *Eunuchism.*

*Case 1.* A single man, aged 20 years. At the age of 13 years his left testis, and at the age of 14 years his right testis, were removed for tuberculosis. His voice did not break, he has never had to shave, and during the

<sup>1</sup> Received August 8, 1940.

last few years he has become fatter. He came to the hospital because of a three years' history of periods of loss of sense of reality, which would come on quite suddenly once or twice a week at any time of the day or night; he would not actually lose his memory, but he would repeatedly say to himself 'I am I'. The attacks were usually accompanied by giddiness and nausea or vomiting, and would last for periods varying from a few minutes to several hours. Being frightened of talking, he would go to bed and the next day would wake up feeling quite well. He was frightened of the dark, and would often have the feeling of a lump in his throat. He was seen in the Psychiatric Department by Dr. E. B. Strauss, who referred him to the writer.

He is the youngest of seven siblings, and has an elder brother who is impotent.

On examination he was moderately intelligent, well covered, but not obese. Height, 5 ft. 8 in.; weight, 9 st. 4 lb. His voice was not broken. There was no growth of hair on the face, in the axillae, or on the chest; the pubic hair was of feminine distribution. His penis was smaller than normal, the scrotum was normal, the testes absent, and the prostate just palpable. The remainder of the physical examination was normal. X-ray examination of the epiphyses at the wrist, elbow, hip, and knee showed no abnormality. The basal metabolic rate was - 11 per cent.

*Treatment and progress.* As the patient was unable to attend for injections of testosterone propionate, a tablet of 50 mg. of free testosterone, sterilized in boiling water, was implanted in the rectus abdominis muscle by Mr. Rupert Corbett. Within four days he had frequent strong erections throughout the day lasting for 15 to 20 minutes at a time, whereas previously these occurred about once or twice a week and were not fully turgid. When seen six weeks after the implantation, his weight was 9 st. 13 lb., and he reported that his penis appeared to be larger, as it was constantly semi-erect, that the frequency of erections was maintained, that he had occasional nocturnal emissions and that he masturbated two or three times a week, resulting in the discharge of a small amount of secretion. This state of affairs was maintained during the following four weeks, but thereafter the number of erections diminished to two or three a week and he no longer had nocturnal emissions. We may conclude therefore that in this patient testosterone implanted as a tablet exerted its effect for about 2½ months. During this period the peculiar feelings of which he had complained were reduced in frequency, and physically he felt much stronger. Two and a half months after implantation his weight was 10 st. 4 lb., and his penis and prostate had increased slightly in size. Four months after implantation a little hair was growing on his upper lip, and his pubic hair had increased, but retained its feminine distribution; two months later his voice was deeper, but his weight had fallen to 9 st. 12 lb. His psychological disturbances no longer troubled him and he had lost his fear of the attacks.

The therapeutic effect of two types of ointment was then compared—an ointment of free testosterone, 2 mg. per gm., one inch of which expressed from the tube contained approximately 1 mg. of testosterone, and an ointment of testosterone propionate, 10 mg. per gm., one inch of which contained approximately 2.25 mg. of testosterone propionate. The patient was instructed to wash thoroughly the skin of the abdomen or thighs before each application to remove any superfluous grease, and then to rub in daily for 15 min. a measured length of ointment. The daily inunction of a 2½-inch strip of testosterone ointment (2.5 mg. of testosterone) caused after four days about four powerful erections a day. With an amount of ointment containing approximately the

same dose of testosterone propionate (2.5 mg.) erections were not quite so frequent. To produce approximately the same effect as 2.5 mg. of testosterone, 4.5 mg. of testosterone propionate were required. For a period between these two methods of treatment inunction was carried out in the same manner with a bland base, containing, unknown to the patient, no active substance. During this period he had two or three erections a week.

After an interval of some months, during which he was undergoing biochemical investigation without treatment, a clinical trial was made of methyl testosterone by mouth. He was first given non-medicated tablets of the same size and shape as those containing the active substance. With these there was some increase in the frequency of his erections (three or four a week), and on one day he had several throughout the day. Although he thought he was still receiving the same tablets, he was then given the same number of medicated tablets daily, a total daily amount of 100 mg. of methyl testosterone in five divided doses, for one week. After about three days libido was marked, he had three or four powerful erections a day, and during one a small amount of secretion. The dose was then reduced to 50 mg. a day in five divided doses, but three or four erections a day were maintained. With a daily dose of 25 mg. in five doses he had one or two erections a day, and with 15 mg. a day one in about two days.

*Case 2.* An Indian medical practitioner, aged 39 years, married, who until the age of 20 years had bilateral undescended testes with bilateral inguinal herniae. Growth and the development of secondary sexual characteristics proceeded normally. At the age of twenty years the operation for the radical cure of the right inguinal hernia was performed, and the right testis, which was small, was anchored in the scrotum. At the age of 22 years he was found to have azoospermia. At 25 years the left inguinal hernia was repaired and a left orchidopexy performed. One month later emissions, which he had previously had during coitus, no longer occurred, and during the next two years potency and sexual desire, which had been strong, were gradually lost. His skin became dry, and the hair on his face and body, previously quite profuse, almost completely disappeared. He continued, however, to shave daily. Whereas before the last operation he had been lean and weighed under 10 st., during the subsequent four years he became obese, especially round the trunk, pelvis, and thighs, and gained 4 st. in weight. During the last four years his ears would become red and hot when he was in bed or sitting in a warm room, causing much discomfort. He was depressed and worried about his condition.

On examination he was highly intelligent, well developed and obese, the fat being mainly on the chest and abdomen and round the pelvis and thighs. His weight was 14 st. His voice was normal. His muscles were flabby. Hair growth was scanty on his face and in the axillae, and was absent on his chest, arms, and legs; the pubic hair was of feminine distribution. Neither testis was palpable, but in their place were two irregular masses, smaller than a pea, which were probably the atrophied remains of the testis and epididymis. The penis was slightly smaller than normal and the scrotum somewhat retracted.

*Treatment and progress.* The patient proved to be a keen observer of the effects of treatment. He was given at first 100 mg. of testosterone propionate intramuscularly three times a week. Forty-eight hours after the first injection he began to have two or three well-sustained erections during the day and libido returned; during the first week of treatment he had intercourse satisfactorily on three occasions. He no longer felt depressed, and experienced



a sense of well-being. During the second week the tone of his muscles increased, he had slight pain in his nipples, and thought the areola was a little darker in colour. At the end of the third week he asserted that sex consciousness was far too great, and that erections were very frequent throughout the day. The dose was therefore reduced to 50 mg. three times a week. This dose was given for two weeks. During this period libido was very strong, erections were frequent during the day, lasting for a half to one hour, and were particularly liable to occur on visual stimuli; once or twice they amounted almost to priapism. He had intercourse daily, during which two or three drops of secretion were ejaculated. After five weeks he thought that his penis was increasing in size. The tone of his muscles was now marked, and he had cramp-like pains in his legs on walking. In five weeks he had gained 16 lb. in weight.

The dose was now further reduced to 25 mg. three times a week, with the result that erections became normal and were not uncomfortable as before. This in his opinion appeared to be the maintenance dose. The cramp-like pains in his leg muscles disappeared, but he still complained of some 'heaviness' in his legs and forearms when walking. After eight weeks' treatment slight oedema of his legs was apparent, the increased tone of his muscles persisted, he felt stronger, and his general physique was improved, as evidenced by some diminution in his obese appearance and by definite hypertrophy of his muscles, especially of the upper arms and thighs. The redness and burning of his ears when warm persisted. Slight increase of hair growth on the face was observed. After four months this was more marked, but not fully normal; however, the pubic hair was now of male distribution and reached above the umbilicus, the lower abdomen was moderately hairy, the hair on his arms and legs was increasing, and the axillary hair was normal. The penis had increased in size and the scrotum was less retracted. The burning of his ears happened only rarely, such as when he was in a hot room. He stated that he had never been so sex-conscious, and that his mental outlook had quite changed; nothing depressed him, nothing worried him, and he felt pugnacious. His muscles were now 'as hard as iron'. In his own words, 'I am an entirely different man, mentally and physically'. His weight remained steady at 15 st. 2 lb.

After four months' treatment he received orders to join his regiment in India, where he is continuing his injections. It is unfortunate that further observations with other methods of treatment were thus prevented.

#### *Hypogonadism.*

*Case 3.* A single man, aged 19 years, who complained of a high-pitched voice, small genitals, and absence of beard. Puberty did not take place, the penis and testes remained small, the voice did not break, and although hair grew in the pubic and axillary regions none grew on the face.

On examination he was intelligent, tall and thin, somewhat feminine in type, with a good complexion and fine, smooth skin. Height, 5 ft. 11 in.; weight, 8 st. 9 lb. His voice was high-pitched; the larynx was that of a small adult (Mr. F. C. W. Capps). There was no growth of hair on the face and chest, axillary hair was present, and the pubic hair was of feminine distribution. The penis was  $2\frac{1}{4}$  in. long and  $2\frac{1}{4}$  in. in circumference; the scrotum was normal; the testes were small, measuring about  $\frac{3}{4} \times \frac{1}{2}$  in.; the prostate was small and just palpable. X-ray films showed a pituitary fossa which was slightly larger than normal. X-ray examination of the forearm showed that the epiphyses at the elbow joint were united, and those at the wrist ununited.



(union should take place between the ages of 18 and 19 years). The basal metabolic rate was +3 per cent.

*Treatment and progress.* For two weeks he was given intramuscular injections of 50 mg. of testosterone propionate three times a week. About 48 hours after the first injection many erections of short duration occurred, and on the fourth day became still more frequent. The dose was reduced to 25 mg. three times a week, and continued at this level for seven months. With this dose full potency was maintained. After about one month's treatment he had pain in both testes, and the left testis and epididymis increased in size. Three weeks later there was slight enlargement of the right epididymis. The pain in the testes was relieved to some extent by wearing a suspensory bandage. Nocturnal emissions, which were absent before treatment, occurred with moderate frequency. During the third month his voice began to break, and during the fifth the change became complete. Muscular strength was increased; before treatment he was weak and easily vanquished in a wrestling match by his brother who was three years his junior; during the sixth month of treatment his brother was no longer always the winner.

After seven months, treatment was discontinued because of cracking and soreness of the prepuce, which on examination could not now be retracted. Six weeks later circumcision was therefore performed by Mr. Rupert Corbett. At this time his height and weight were unchanged, neither was there any change in the growth of hair. His penis measured  $2\frac{1}{2}$  in. in length and 3 in. in circumference, the right testis  $\frac{3}{4} \times \frac{1}{2}$  in. and the left  $1\frac{1}{2} \times 1$  in. His prostate was more easily palpable. X-ray examination of the wrist, nine months after the beginning of treatment, showed that the lower epiphyses of the radius and ulna were beginning to unite. The basal metabolic rate was -16 per cent.

About one month after circumcision two 50-mg. tablets of testosterone were implanted subcutaneously. About four days later, libido was increased, nocturnal emissions occurred about once a week, erections were frequent throughout the day, but were never uncomfortable, and there was aching of the right testis. His weight increased by 3 lb. in five weeks. He said that he 'felt tough', that he could endure cold weather better, and that his bowels, which had previously acted irregularly, were now normal. He observed no change in mental vigour, but he had more self-confidence. Two months after the implantation his left testis was four times larger than the right, which remained unchanged, his prostate was definitely larger and his voice was deeper. The action of the tablets, as judged by the frequency of erections, appeared to have ceased after two months.

Three months after the implantation he was instructed to rub daily into the skin of his abdomen or thighs a 3-in. strip of testosterone propionate ointment, approximately 7 mg. of testosterone propionate. He used this for 12 days. Six days after beginning inunction libido was greatly increased, and erections were more frequent than when he was given 25 mg. of testosterone propionate intramuscularly three times a week. After an interval of two weeks he was instructed to rub daily into his skin 3.5 c.c. of an alcoholic solution of testosterone propionate, 2 mg. per c.c., i.e. 7 mg. of testosterone propionate. After four days a response was obtained, but the erections were not quite so frequent as with the ointment. He felt very pugnacious and had a fight with his brother. A peculiar feature which this method of administration produced was a 'doped and sleepy feeling', which caused him to discontinue after a week.

Thereafter he resumed injections of 25 mg. of testosterone propionate

three times a week for three months, when they were discontinued owing to his leaving England. At the end of this treatment his voice was very much deeper and firmer, and Mr. Capps reported that his larynx had developed remarkably and was now wide and fully formed. Hair grew on his upper lip and chin, necessitating shaving about once a week; there was increased growth of hair on the thighs, and the pubic hair was tending to grow upwards to the umbilicus. His penis measured  $3\frac{3}{8}$  in. in length and  $3\frac{1}{8}$  in. in circumference (Plate 17, Figs 1 and 2), the left testis was about  $1 \times 1\frac{1}{2}$  in. and the right  $\frac{3}{4} \times \frac{1}{2}$  in. His weight was 10 st. 6 lb., having increased by 25 lb. during the last nine months, i.e. since the implantation of the tablet of testosterone. Three months after stopping treatment he wrote saying that potency, libido, and muscular strength were maintained, but that the growth of hair on his face and abdomen had diminished.

*Case 4.* A boy, aged 16 years, with delayed puberty. His voice was not breaking, secondary sexual hair was not appearing, his penis and scrotum were infantile, and his testes small. His general physical development was normal. His weight was 7 st. 12 lb.

*Treatment and progress.* For the first month he was given 25 mg. of testosterone propionate intramuscularly twice a week, and thereafter, because he was unable to attend more frequently, 50 mg. once a week. Treatment was given for five months. With 25 mg. twice a week erections did not occur, but with 50 mg. once a week were fairly frequent. After two months his voice began to break. After five months his penis had greatly increased in size and could now be considered normal, the testes were larger and the scrotum lax; growth of pubic hair was moderate and of axillary hair slight; there was no growth of hair on his face. Muscular strength was increased. His weight was 8 st. 6 lb. Owing to the war, treatment and observation had to be discontinued.

*Case 5.* A single man, aged 20 years, who complained of small genitalia. At the age of 18 years he grew a slight amount of hair on his face, and shaved on alternate days. On examination, he looked younger than his years; he was plump, with an abdominal pad of fat and wide hips of feminine type. There was no growth of hair on his face and chest, and it was scanty in the axillae and on the pubes, where it was of female distribution. The penis was small, and the testes small and retractile. His weight was 12 st. 6 lb. X-ray examination showed that the pituitary fossa was normal, and that the epiphyses at the lower end of the radius and ulna were ununited.

*Treatment and progress.* He was treated for six weeks with 100 mg. of testosterone propionate intramuscularly twice a week. About two days after the first injection, erections increased in frequency and duration, and in fact they were more or less constant throughout the day. After six weeks his penis could be considered normal in size, and the testes were permanently in the scrotum and had increased to two or three times their previous size. His voice was deeper, and there was slightly increased growth of hair on the face, but the pubic hair was still of feminine distribution. Libido was not increased nor did he feel pugnacious, but he felt 'bigger and stronger'. His weight increased by 1 lb. Treatment had to be discontinued when he was called up for military service.

*Case 6.* An Indian, aged 29 years, single, who complained of under-development. He developed normally until the age of 15 years. From that time

he appeared younger than his years; his voice did not break; at the age of 19 years pubic hair began to appear, but growth in the axillae was scanty and was absent on his face. His penis and testes remained small, and erections were rare. At the age of 27 years he was treated in India with injections of 'anterior pituitary extract'; the result was a transient interest in the opposite sex, which he had not previously felt. At the age of 28 years the left vas deferens was ligatured in Vienna, and this was followed by 'a course of sixty injections of testosterone propionate'. As a result he had frequent erections, but genital development was unaffected; he gained 20 lb. in weight.

On examination, he was intelligent, thin, and of slender build. His weight was 8 st. 6 lb. He appeared to be aged about 19 years. His voice was not quite broken; his face and trunk were free from hair, except on the pubes, where it was of female distribution; his hips were of female type. His penis was 2 in. long, and the testes measured  $\frac{3}{4} \times \frac{1}{2}$  in. X-ray films of the pituitary fossa were normal; X-ray examination of the epiphyses of the long bones showed that the epiphyseal lines in the region of the knee joints were just visible, evidence of delayed union. The basal metabolic rate was - 30 per cent.

*Treatment and progress.* A 50 mg. tablet of testosterone was implanted under the left lower rectus abdominis muscle by Mr. Rupert Corbett. On the second day he had three well sustained erections, and for the next two weeks erections were practically continuous; thereafter their number was reduced to three or four a day. His basal metabolic rate two weeks after the implantation was - 32 per cent. Six weeks after implantation the tablet was discharged through the scar of the incision. The weight of the discharged tablet was 15 mg.; hence 35 mg. of testosterone were absorbed during six weeks. His weight had increased to 9 st. He was then treated with intramuscular injections of 50 mg. of testosterone propionate twice a week for two months. With these, erections were as frequent, but not as powerful, as they were during the second fortnight after implantation of the tablet. Unfortunately treatment had to be discontinued, as the patient had to return to India. At this time his voice was a little lower and his penis slightly larger, but the growth of hair was unchanged. He appeared to have no alteration in mental outlook or increase in muscular strength. His weight was 9 st. 2 lb.

#### Discussion

*Results of treatment.* The case reports of these six patients with deficient testicular function demonstrate the effectiveness of treatment with testosterone, whether it be given by implantation in the form of tablets, or by injection, or as the propionate by intramuscular injections. In the main it brought about normal potency and libido, increased growth of the penis, scrotum, and prostate, increased growth of hair on the face, trunk, pubes, and limbs, and breaking of the voice, associated in one patient (Case 3) with development of the larynx to normal adult proportions. The depression or sense of inferiority, from which most patients suffered as a result of their deficiencies, disappeared and was replaced by a feeling of physical and mental well-being, and in some patients even pugnacity. The more pronounced psychological disturbance, which caused Case 1 to seek medical advice, and which may have been due to a feeling that he was different from other men,

was greatly improved after implantation of a tablet of testosterone, and ultimately cleared up completely.

The first evidence of action of the hormone was the rapidly increasing frequency, degree, and duration of erections, which occurred about 48 hours after the first injection of testosterone propionate, between two and four days after implantation of a tablet of testosterone, and about four days after incision. In most cases the sense of well-being appeared soon after potency was established. During the second or third month of treatment increased growth of the penis began to be manifest, but in the early stages it was difficult to be certain of this owing to its frequently semi-erect condition. Breaking of the voice took place between the second and fifth month in those in whom this had not occurred. About the same time most patients began to be aware of increased muscular strength. In Case 2 flaccidity of the muscles, which was apparent before treatment, was replaced after three weeks by increased tone, which later became very marked and was accompanied by cramp-like pains in the legs on walking. These pains did not arise in other patients. Increase in the bulk of the muscles of the extremities, particularly of the thighs and upper arms, was very definite in this patient. This is in accordance with the experimental findings of Papanicolaou and Falk (1938), who produced general muscular hypertrophy with testosterone propionate in castrated immature male and in spayed and normal adult female guinea-pigs, an effect which they did not obtain with oestrogenic hormones. As these authors have suggested, the greater muscular development of the male may be dependent on the action of the male sex hormone. Kenyon, Sandiford, Bryan, Knowlton, and Koch (1938) have reported that in the eunuchoid testosterone propionate consistently causes a striking reduction in the urinary total nitrogen, which is reflected completely in the urinary urea and is unaccompanied by any increase in the nitrogenous constituents of the blood. They considered that it is highly possible that some of the nitrogen retained is stored in the muscles. The increase in muscular tissue in this patient would support this view.

Increased growth of hair on the face, trunk, and limbs was one of the later secondary sexual characteristics to appear, but in no case can it be said to have attained full male distribution. This is in accordance with all reports that have come to my notice. In Cases 1, 4, 5, and 6 treatment was not continued for a sufficiently long period, but in Case 3, who was treated for 18 months, although hair growth was stimulated, that on his face was never enough to warrant shaving more frequently than once a week and the pubic hair retained its female distribution. The best response was obtained in Case 2, whose pubic hair had assumed male distribution at the end of four months' treatment, but even in him the growth of the beard during the four months that he was under observation fell short of the normal adult male. It is not improbable, however, that in his case further treatment may have repaired this deficiency. It was observed that cessation of treatment caused the hair growth to retrogress (Case 3).



In Case 3, in whom there was delay in union of the epiphyses, the lower epiphyses of the radius and ulna were beginning to unite after nine months' treatment. Curiously enough, in the prepuberal eunuch (Case 1) there appeared to be no delay in fusion of the epiphyses. In two other patients (Cases 5 and 6) in whom there was evidence of delayed union, no change was observed after 6 weeks and 3½ months' treatment respectively. If testosterone is a factor in hastening epiphyseal union, it appears that prolonged treatment is necessary, for Villaret, Justin-Besançon, and Rubens-Duval (1938) found no change after six months' treatment, and Turner (1939), using doses of 10 mg. three times a week, obtained negative results after 11 months.

An interesting feature was the oedema of the legs which appeared in Case 2. Kenyon (1938) observed in four eunuchoids treated with testosterone propionate fullness and puffiness of the face in all, puffiness of the hands in one, and pitting oedema of the legs in another. Thorn and Harrop (1937) found in normal dogs that testosterone, oestradiol, progesterone, and pregnandiol exerted an effect similar to the adrenal cortical hormone in that they caused retention of sodium, and consequently of water. Kenyon, Sandiford, Bryan, Knowlton, and Koch (1938) and Kenyon, Knowlton, Sandiford, Koch, and Lotwin (1940) confirmed this effect of testosterone in man when they found a fall in urinary sodium and chloride in eunuchoids, normal men, and a normal woman treated with testosterone propionate, and associated these findings with the oedema which is sometimes observed in patients thus treated.

Gain in weight occurred in all patients—14 lb. in 2½ months in Case 1, 16 lb. in 5 weeks in Case 2, 25 lb. in 18 months in Case 3, 8 lb. in 5 months in Case 4, 1 lb. in 6 weeks in Case 5, and 10 lb. in 3½ months in Case 6. Case 3 was unusual in that he gained no weight during the first seven months of treatment, but only during the last nine months. Kenyon, Sandiford, Bryan, Knowlton, and Koch (1938) have shown that the gain in weight is due largely to the water retained in association with sodium and nitrogen.

Of the four patients with palpable testes, testosterone propionate had an effect on three. In Case 3 pain was felt in both testes, and there was slight enlargement of both epididymes and a fourfold increase in the size of the left testis; there did not appear to be any definite increase in the size of the right testis. In Cases 4 and 5 both testes increased in size, and the retractile testes of Case 5 remained permanently in the scrotum. Reports of the action of testosterone propionate on the testes, clinically and experimentally, are at variance. Kenyon (1938) observed no increase in the size of the testes in four patients treated, but Hamilton (1937) reported growth of the epididymis, and Kunstadter (1938), Vest and Howard (1938), Villaret, Justin-Besançon, and Rubens-Duval (1938), Turner (1939), and Eidelsberg and Ornstein (1940) have all reported growth of the testes during treatment. It is doubtful whether this is due to direct stimulation of the testes, or to growth of the scrotum, induced by testosterone propionate, favouring testicular development. The observations of Rubinstein and Kurland (1939) of increased spermatogenesis in sterile, but otherwise normal, men treated with small doses

of testosterone propionate (5 mg. three times a week) support the view that its action may be one of direct stimulation. It is noteworthy that these authors found that larger doses of 25 mg. three times a week suppressed spermatogenesis, suggesting that its influence on the testes is a question of dosage. Experimentally testosterone prevents the atrophy of the testes which follows hypophysectomy (Nelson and Gallagher, 1936), but in normal immature animals, although several observers have reported that testosterone propionate stimulates spermatogenesis, the majority have found that it causes atrophy of the testes (Bottomley and Folley, 1938; Moore and Price, 1938; and Zuckerman, 1938).

It is well known that vasomotor disturbances occur in patients with gonadal deficiency. Case 2 illustrates this, and the diminution of his flushes with testosterone propionate is in accordance with the findings of other observers. The pain in the nipples which this patient experienced for a short time early in his treatment is analogous to the same phenomenon which is so common at puberty. Although not evident in this patient, probably because of his obesity, hypertrophy of breast tissue has been observed in man and in animals treated with androgens (Kenyon, 1938). The administration of testosterone propionate causes, in addition to an increased urinary excretion of androgen, an increased excretion of oestrogen (Steinach and Kun, 1937; Callow, Callow, and Emmens, 1939), but whether this 'mastitis' is due directly to testosterone or to oestrogen is unknown.

*Comparison of the effectiveness of different preparations.* In animals one may obtain a fairly accurate measure of the effectiveness of different androgens and of various modes of administration by objective observations, such as the growth of the capon's comb and the increase in weight of the prostate and seminal vesicles of the rat. In man there is no such convenient and accurate method, and as a short-term experiment is alone feasible, one must necessarily rely on the frequency and potency of the erections produced. This is obviously not entirely satisfactory, for one is wholly dependent on the observations of the patient, and psychological influences probably give rise to some inaccuracy. Bearing this in mind one must exercise caution in drawing conclusions. By treating all the patients with the various preparations, as was originally proposed, a more accurate comparison would have been obtained. This was unfortunately prevented by the patients having to join the forces or to leave London as a result of the war.

*Intramuscular injections of testosterone propionate.* This method is the one which has been most widely used. In the cases reported here doses of 100 mg. and 50 mg. three times a week produced very frequent and prolonged erections, often with considerable discomfort, necessitating a reduction in dosage. I feel, however, that these higher doses are necessary at the beginning of treatment in adult patients in order rapidly to restore sexual function. Thereafter the dose is reduced to a maintenance dose, which appears to be a weekly total of 50 to 75 mg., given in two or three injections. With this amount potency and libido are still somewhat above normal, but this is not undesirable when



an endeavour is being made to hasten the appearance of secondary sexual characteristics. Once these have developed the dose would probably be less than 50 mg. per week.

*Percutaneous administration.* In Case 1 the daily inunction of ointment containing 4.5 mg. of testosterone propionate produced about four powerful erections a day, and in Case 3 potency was in excess of normal with the daily inunction of 7 mg. These amounts are very much lower than Foss (1938, 1939 a) found necessary in a eunuch, who required at least three applications of 25 to 30 mg. during the week. These figures demonstrate that individual requirements appear to vary considerably. Contrary to Moore, Lamar, and Beck (1938), Deanesly and Parkes (1937) found that in the rat inunction was not a very efficient method of administration, but that in the capon comb test direct inunction was about 200 times more effective than intramuscular injection. In my patient, Case 3, a total dose of 49 mg. a week given by daily inunction produced a greater effect than 75 mg. a week given in three intramuscular injections. I am in agreement with Foss that inunction of testosterone propionate as a tincture is not quite so effective as an ointment.

Moore, Lamar, and Beck (1938), judging from the weight of the seminal vesicles of castrated rats, found that inunction of free testosterone ointment was more than twice as effective as inunction of an ointment of testosterone propionate. In Case 1 daily inunction of 4.5 mg. of testosterone propionate produced about the same effect as daily inunction of 2.5 mg. of testosterone. This lesser effectiveness of testosterone propionate is probably due to its very slow absorption by inunction.

*Implantation of tablets.* The duration of action of one or of two 50 mg. tablets of testosterone implanted subcutaneously or intramuscularly appeared to be between eight and ten weeks (Cases 1 and 3). This clinical judgement is in agreement with actual measurements. In Case 6, in whom the tablet was discharged after six weeks, 35 mg. had been absorbed during this period, so that the whole tablet would have been absorbed in a little over eight weeks. The implantation of a tablet causes a very marked response, but has the disadvantage that this cannot be controlled. It is, however, the cheapest and a very convenient form of therapy. No advantage is obtained by inserting more than one tablet, for the duration of action is not of course prolonged and the response obtained with one tablet is more than adequate.

*Oral administration of methyl testosterone.* It has been shown in castrated rats that by injection in oily solution methyl testosterone has a greater potency than testosterone (Deanesly and Parkes, 1936), and that the oral activity of methyl testosterone is about two-fifths of its activity when given by injection (Emmens and Parkes, 1939). Foss (1939 b) has observed in a eunuch that methyl testosterone is about twice as active by mouth as testosterone, and he obtained full potency with 100 mg. and moderate potency with 50 mg. daily. In the one patient (Case 1) of the present group in whom it has been used, full potency was maintained with a daily dose of 50 mg. and moderate

potency with 25 mg. No evidence of toxicity was observed. In this patient 50 mg. of methyl testosterone daily by mouth produced about the same effect as the daily inunction of 2.5 mg. of testosterone. If methyl testosterone can be manufactured moderately cheaply, it should be an effective and most convenient method of therapy.

#### Summary

1. Two patients with eunuchism and four with hypogonadism were treated with intramuscular injections of testosterone propionate, implantation of tablets of testosterone, inunction of testosterone propionate as an ointment or tincture, inunction of testosterone as an ointment, or the oral administration of methyl testosterone.

2. In all the patients treatment established potency and caused increased growth of the penis and scrotum, deepening of the voice and gain in weight, and in five patients increased growth of hair on the face, body, and limbs. In several it caused disappearance of psychological disturbances, improvement in mental outlook, pugnacity, increased libido, increased muscular strength, and increased growth of the testes and prostate. In individual patients it hastened union of the epiphyses and caused normal development of the larynx, tenderness of the nipples, muscular hypertrophy, and oedema of the legs.

3. The effectiveness of each preparation has been demonstrated. The maintenance doses required to produce about the same effect, as judged by the frequency and potency of erections, were: (1) Testosterone propionate intramuscularly, 50 to 75 mg. per week, given in two or three injections. (2) Daily inunction of testosterone propionate as an ointment, 32 to 49 mg. per week. (3) Daily inunction of testosterone as an ointment, 17.5 mg. per week. (4) Oral administration of methyl testosterone, 350 mg. per week in doses of 10 mg. five times a day.

Free testosterone implanted as a 50-mg. tablet exerted its action for 8-10 weeks.

I am greatly indebted to Messrs. Ciba Ltd. for generous supplies of testosterone propionate (Perandren), testosterone (Perandren) ointment, testosterone propionate ointment and tincture, and methyl testosterone, and to N. V. Organon for generous supplies of testosterone propionate (Neohombreol) and tablets of testosterone for implantation.

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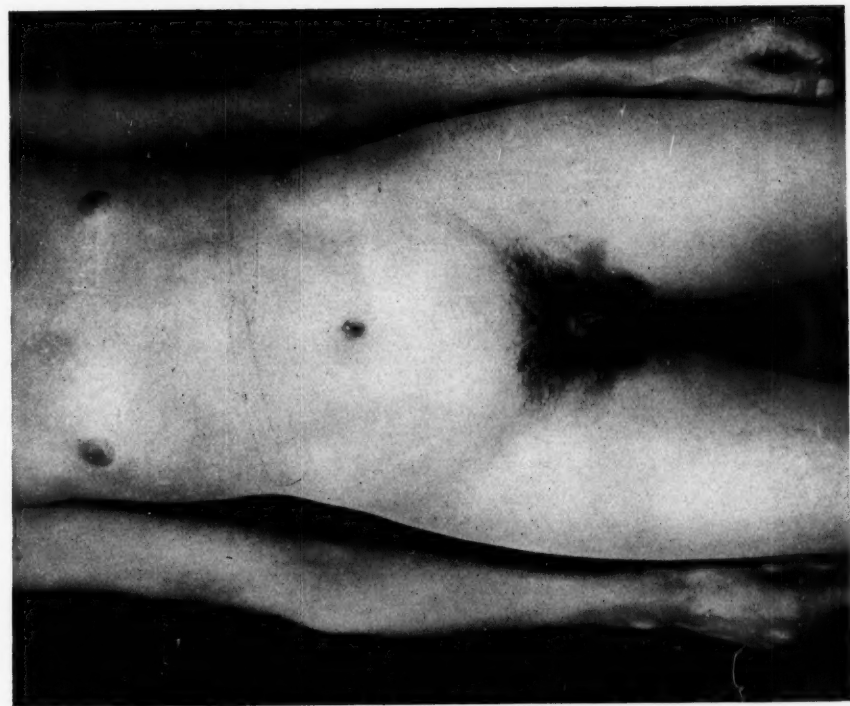


FIG. 1  
Case 3, before treatment

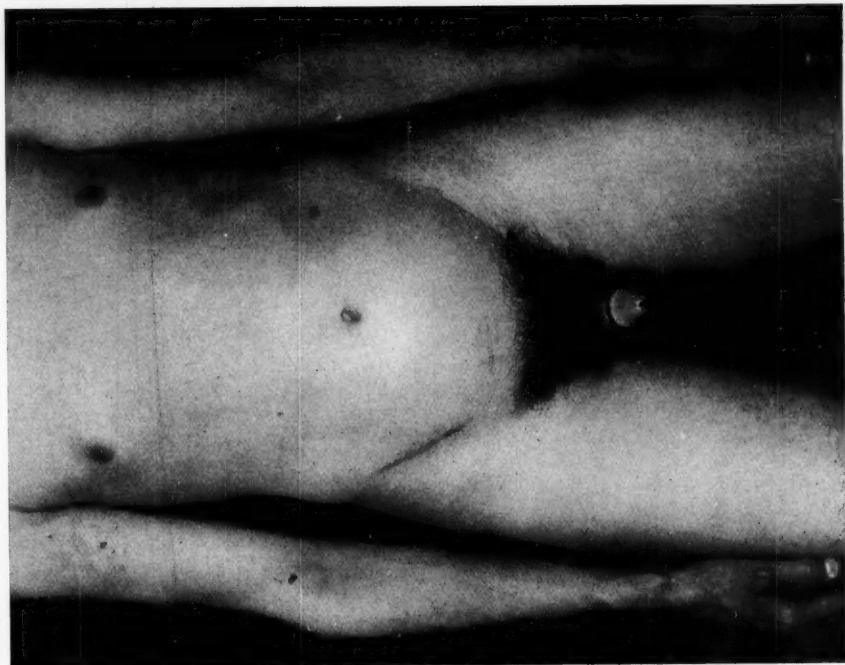


FIG. 2  
Case 3, after treatment for 15 months, showing increased growth of  
penis and pubic hair

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## THE LATE RESULTS OF ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS<sup>1</sup>

By B. R. CLARKE AND S. L. W. ERSKINE

THIS paper is a study of the results of the treatment of 400 patients in whom artificial pneumothorax was attempted between January 1925 and December 1933. These patients were treated in the Forster Green Hospital and a diagnosis of pulmonary tuberculosis had been made in every case. Tubercle bacilli were demonstrated in the sputum in 389 patients (97 per cent.). There was X-ray evidence of cavitation in 358 patients (88 per cent.). All the patients had well marked signs of active disease, and many of them had far advanced disease with involvement in the 'good' lung. The patients were drawn from the urban and rural districts of Northern Ireland in about equal proportions. The majority of them belonged to the working classes (small farmers, labourers, artisans, and mill-workers), while a minority belonged to the middle classes. Northern Ireland is a small community and it has been possible to trace the history of 99 per cent. of these patients to the end of 1938; that is, at least five years from the date when the collapse of the lung was effected or attempted. The statistical tables include all the patients, not omitting those in whom the treatment was abandoned as useless in a short time or was attempted without any success.<sup>2</sup> In presenting the results it was not considered advisable to subdivide the cases according to age or sex. The numbers of men and women in the series were approximately equal and the great majority of patients were between 20 and 40 years of age when the treatment was begun. The youngest patient was 14 and the eldest 55 years.

We have classified the patients according to the degree of collapse obtained into 3 groups:

(1) *Satisfactory collapse* (S.C.). This implies good relaxation of the lung tissue over all obviously diseased areas and disappearance of cavities. Cases of 'black lung', presumably due to atelectasis, have been classified as S.C. if the lung is well collapsed. As very few cases in this series were treated by internal pneumolysis a complete hilar collapse has only rarely been obtained.

(2) *Not satisfactory collapse* (N.S.C.). This implies failure of cavities to close and poor relaxation of obviously diseased areas.

(3) *No collapse* (N.C.). In this group no pleural space could be found, or only a small pocket which was not large enough to be maintained.

Everybody recognizes that better results are obtained when the collapse

<sup>1</sup> Received June 20, 1940.

<sup>2</sup> Ten cases which had artificial pneumothorax as a temporary measure in the treatment of haemoptysis are excluded.

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is satisfactory, but the significance of this observation has been variously assessed. Unsatisfactory collapse is usually associated with adhesions, but the use of the thoracoscope has taught us that a cavity may fail to collapse after all adhesions have been divided. This failure may persist for many months and is of ominous significance. In the present series only a very small number (10 patients) had pleural adhesions divided by surgery, but a considerable number had phrenic evulsion performed during the later years of the period under review.

*Phrenic evulsion and artificial pneumothorax.* Of the 400 patients, 181 had phrenic evulsion done on the same side as that on which the artificial pneumothorax had been induced or attempted. Only 28 of the 152 patients who had artificial pneumothorax between 1925 and 1930 had phrenic evulsion (18 per cent.), while 153 of the 248 patients induced in 1931 to 1933 had the operation (62 per cent.). The results of treatment were much better during these last three years, both as regards the proportion of patients with a good collapse and the survival of all groups of patients, irrespective of the efficiency of the collapse. There is no obvious reason for the improved results except the associated phrenic operation, and therefore it has been considered worth while to tabulate the results separately for these two periods. The commonest indications for phrenic evulsion were unsatisfactory collapse and complete failure of the lung to collapse. A number of cases also had phrenic evulsion performed before the termination of a satisfactory pneumothorax. Purce and Clarke (1936) studied the results of phrenic evulsion combined with artificial pneumothorax.

'Phrenic evulsion was performed in 178 cases with a more or less successful artificial pneumothorax. However, in 66 patients the lung was already satisfactorily collapsed before phrenic evulsion was done. In 25 patients phrenic evulsion was performed after an unsuccessful artificial pneumothorax had been discontinued. There remain 87 patients to be considered who had an unsuccessful artificial pneumothorax (the chief criterion of which was an uncollapsed cavity) at the time phrenic evulsion was performed. A temporary improvement in the collapse followed phrenic evulsion in almost every case, and collapse became satisfactory in 35 patients (3 of whom had adhesions cut as an additional measure). The remaining 52 patients did not attain a satisfactory collapse, although usually cavities appeared smaller after the operation.'

The time factor is of extreme importance in artificial pneumothorax, for success is probable when treatment is begun during the first months of the disease and improbable when treatment is begun too late. Table V illustrates the importance of the time factor.

*Bilateral collapse.* A number of the patients had bilateral pneumothorax, either simultaneous collapse of both lungs or consecutive collapse. Some patients also had artificial pneumothorax on one side and phrenic evulsion or phrenic crushing on the other side. The collapse, or attempted collapse, of the second lung has been ignored in compiling the tables.

TABLE I

*400 Artificial Pneumothorax Cases, 1925 to 1933.**Classification of Collapse.*

	S.C.	N.S.C.	N.C.	Total.
1925 to 1930 (18 % with phrenic evulsion)	36	85	31	152
1931 to 1933 (62 % with phrenic evulsion)	95	99	54	248
Total	131	184	85	400

TABLE II

*400 Artificial Pneumothorax Cases, 1925 to 1933.**After Results to 31 December 1938.**(5 to 14 years).*

	Alive and well.	Alive.	Dead.	Untraced.	Total.
S.C.	89	11	29	2	131
N.S.C.	39	13	131	1	184
N.C.	28	6	50	1	85
Total	156	30	210	4	400

TABLE III

*Analysis of Deaths 'Within 5 Years of Induction' of Artificial Pneumothorax.*

	1925 to 1930 (18 % with phrenic evulsion).	1931 to 1933 (62 % with phrenic evulsion).	Total deaths, 1925 to 1933.
S.C.	25 % (9)	16 % (15)	18 % (24)
N.S.C.	70 % (63)	53 % (53)	63 % (116)
N.C.	71 % (22)	42 % (22)	52 % (44)
Total	62 % (94)	36 % (90)	46 % (184)

TABLE IV

*Results 1925 to 1930—8 to 13 Years Later.*

	Alive and well.	Alive.	Dead.	Untraced.	Total.
S.C.	23	2	11	—	36
N.S.C.	12	2	71	—	85
N.C.	6	1	24	—	31
Total	41	5	106	—	152

TABLE V

*To Show the Relation Between Duration of Disease and Successful Collapse.*

Duration of disease before artificial pneumothorax.	S.C.	N.S.C.	N.C.	Total.
Less than 6 months	68 (55 %)	40	16	124
Six to 12 months	26 (28 %)	48	19	93
More than 12 months	37 (20 %)	96	50	183
Total	131	184	85	400

*Satisfactory Collapse (131 patients).*

Tubercle bacilli were found in the sputum on admission in 121 of these patients, in 10 patients the sputum was negative. On discharge tubercle bacilli were present in 21, in 110 the sputum was negative. There was radiological evidence of cavitation in 108 patients on admission, in 23 patients no such evidence was found.

*Duration of Pneumothorax in Years.*

0 to 1.	1 to 2.	2 to 3.	3 to 4.	More than 4.	Total.
29	32	33	29	8	131

*Phrenic Evulsion and Pneumolysis.*

Of the 131 patients phrenic evulsion was performed in 63 and intrapleural pneumolysis in 10.

*Late Results.*

Ninety-six of the 131 patients were examined and X-rayed after expansion of the collapsed lung had taken place. The intervals which elapsed between the expansion of the lung and the radiological examination were as follows:—

0 to 1 year.	1 to 2 years.	2 to 5 years.	More than 5 years.	Total.
29	24	34	9	96

Eighty-two of the 96 patients examined were in good health and had no evidence of active disease in either lung, 3 had active disease in the 'pneumothorax' lung, 6 had active disease in both lungs, and 5 had active disease in the contralateral lung. Of the 14 patients who had active disease at the time of re-examination 8 have since died.

Six of the 35 patients who were not radiologically examined after expansion of the lung are known to be in good health, 6 are alive and in fair health, 2 are untraced, and 21 are dead.

*Effect of Artificial Pneumothorax on Cavities.*

No cavity.	Cavity 'healed'.	Cavity 'not healed'.	Cavity not seen.	Total.
15	64	9	8	96

*Condition of 'Pneumothorax' Lung after Expansion.*

Normal.	Fibrosis +.	Fibrosis ++.	Active disease.	Total.
2	50	35	9	96

*Condition of Contralateral Lung.*

Normal.	'Healed' lesion.	Active disease.	Total.
64	21	11	96

*Displacement of Mediastinum to 'Pneumothorax' Lung.*

None.	+	++	Total.
34	35	27	96

Of the 29 patients who died (Table II), 1 died of tuberculous meningitis, 1 of intestinal tuberculosis, 1 of transverse myelitis, 1 of spontaneous pneumothorax, and 1 of empyema. In 10 patients the cause of death appeared to be the spread of disease in the contralateral lung, and in 1 patient spread of disease in the pneumothorax lung. Three patients died of non-tuberculous causes, and in 10 the exact cause was unknown, but was presumed to be tuberculosis.

In the opinion of the writers the late results are encouraging in the S.C. group, considering the social circumstances of the patients and the fact that technique was imperfect in the earlier years under review. Thus, 29 of the S.C. cases had an artificial pneumothorax for less than twelve months and in about half of these the quick termination of the artificial pneumothorax was due to obliteration of the pleural space. With improved technique, and particularly by maintaining short intervals between refills, this premature obliteration has occurred only rarely in recent years.

The proportion of S.C. cases has been substantially increased by combining artificial pneumothorax and phrenic evulsion (see Table III). Only 25 per cent. of the total cases attempted had a satisfactory collapse in the earlier period, 1925 to 1930, while 38 per cent. had a satisfactory collapse in the later period, 1931 to 1933, when phrenic evulsion was frequently employed to improve the collapse. Only 10 patients in this series had intrapleural pneumolysis, and the wider application of this operation has improved the results during the past six years (which are not reviewed in this paper). In spite of this improvement, a high proportion of failures remains and this is the most disappointing feature of treatment with artificial pneumothorax. Many published results are not comprehensive, and omit the failures and those who had artificial pneumothorax for a short time only. Three important series of results have been reported by Matson, Matson, and Bisaillon (1923), Edwards (1939), and Sinding-Larsen (1937).

	S.C.	N.S.C.	N.C.	Total.
Matson, Matson, and Bisaillon	235	245	120	600
Edwards	426	758	432	1616
Sinding-Larsen	164	505	352	1021
Present series	131	184	85	400

All these figures indicate that in the past a satisfactory collapse has been achieved in less than half the patients treated. The outstanding cause of failure is delay in beginning treatment, and this is illustrated clearly by Table V. In those patients who had artificial pneumothorax within six months of the onset of their illness a good collapse was obtained in 55 per cent.; in those whose illness was of more than 12 months' duration only 20 per cent. showed a satisfactory result. As Burrell (1931) said:

'At present it is usual not to collapse the diseased lung in an early acute case unless the patient fails to improve under simple medical treatment; but cases are now treated by collapse much earlier than they were a few years ago, and I think that in the near future all early cases of unilateral disease will be treated by pneumothorax unless there is some definite contra-indication. When once crepitations are heard the case cannot be regarded as in the really early stage, and certainly pneumothorax should be advocated. It is only waste of time to try other methods because, although it is true that some do well, many do not, and even those who do well at first are very liable to relapse, and it is often found that it is then too late for pneumothorax to have its full effect, either because the pleura has become adherent or because the disease has spread to the other lung.

'In advanced fibrotic cases pneumothorax has not the same advantages. It is sometimes possible to collapse a cavity, and if it is not collapsed at first it may become so after cauterization of adhesions, but in my series of cases those with old disease did not do nearly so well with pneumothorax as did the early cases. It seems to me that pneumothorax will be used more and more in the early and acute case and thoracoplasty in the chronic fibrotic one.'



Practical steps require to be taken to ensure that treatment is applied without delay in the suitable case. It would be beyond the scope of this paper to discuss the indications for artificial pneumothorax, but, in the writers' opinion, the treatment should be applied to the great majority of patients with a positive sputum and radiological evidence of a cavity. In a small proportion of these cases it is justifiable to wait for some months in the hope that healing will occur without artificial pneumothorax and, if the patient is kept at strict rest, the chance of such healing will be increased. It is also probable that pleural adhesions are less likely to form over the diseased areas when a patient is at rest in bed.

#### *Not Satisfactory Collapse (184 Patients).*

Tubercle bacilli were found in the sputum on admission in every case. On discharge, tubercle bacilli were present in 167; in 17 the sputum was negative. There was radiological evidence of cavitation in 175 patients on admission; in 9 patients no such evidence was found.

#### *Duration of Pneumothorax in Years.*

0 to 1.	1 to 2.	2 to 3.	3 to 4.	More than 4.	Total.
140	25	11	4	4	184

#### *Phrenic Evulsion and Thoracoplasty.*

Of these 184 patients phrenic evulsion was performed in 61, phrenic evulsion and thoracoplasty in 7, and in one thoracoplasty alone.

#### *Late Results.*

Of the 52 patients who are known to be alive phrenic evulsion had been performed in 22, phrenic evulsion and thoracoplasty in 7, and in one thoracoplasty alone.

The total number of N.S.C. cases is 184, as compared with 131 cases with satisfactory collapse. This illustrates the serious role played by adhesions in preventing the collapse of diseased areas of lung. The percentage of cases with N.S.C. decreased from 56 in the earlier group, 1925 to 1930, to 40 in the later group, 1931 to 1933, and this improvement is attributed to increased use of phrenic evulsion. The death-rate in the N.S.C. group is higher than the N.C. group, and no doubt this is partly due to the fact that some seriously ill patients in this group were unable to continue the treatment long enough to obtain a good collapse, or were unfit to undergo the operation of phrenic evulsion. It is, however, impossible to avoid the conclusion that the partial, contraselective artificial pneumothorax was harmful to some of these patients, and this may explain in part why the patients in this group fared worse than those with no collapse at all. Table III shows that the N.S.C. group fared much better when artificial pneumothorax was combined with phrenic evulsion. Forty-four patients in this group were given artificial pneumothorax refills for more than a year. The classification as regards collapse was done at the time of discharge from hospital and a number of these patients attained a satisfactory collapse shortly afterwards. The artificial pneumothorax was continued in other cases because the patients showed a marked improvement



in spite of the poor collapse. It is, however, doubtful whether this improvement was brought about by the partial artificial pneumothorax. The heavy mortality in the N.S.C. group, especially in the earlier years before phrenic evulsion was employed, emphasizes the importance of considering alternative methods of collapse. It is probably good practice to stop an unsatisfactory artificial pneumothorax after a few weeks if there is no prospect of improving the collapse by operation.

#### *No Collapse (85 Patients).*

Tubercle bacilli were found in the sputum on admission in 84 patients; in one the sputum was negative. On discharge tubercle bacilli were present in 69 patients; in 16 the sputum was negative. There was radiological evidence of cavitation in 75 patients on admission; in 10 patients no such evidence was found.

#### *Phrenic Evulsion and Thoracoplasty.*

Of the 85 patients phrenic evulsion was performed in 46, phrenic evulsion and thoracoplasty in 3, and in one thoracoplasty alone.

#### *Late Results.*

Of the 34 patients who are known to be alive phrenic evulsion had been performed in 24, phrenic evulsion and thoracoplasty in one, and in one thoracoplasty alone.

These cases fared better than the N.S.C. group, but worse than the S.C. group. Table III shows a marked improvement during the later years, 1931 to 1933, presumably due to the increased use of phrenic evulsion and thoracoplasty. In these later years almost two-thirds of the N.C. cases were alive five years after the failure to induce an artificial pneumothorax, and the majority of these survivors were fit for work. Prolonged rest treatment combined with phrenic evulsion or apical thoracoplasty will restore many patients to health, even after artificial pneumothorax has failed. The most striking conclusion drawn from the mortality tables is that the results are very much better for the S.C. group than for the other groups. It is also clear that the N.S.C. group has fared worse than the N.C. group, and possible explanations of this have been discussed.

Saugman (1921) was one of the first to point out that the results of artificial pneumothorax depended entirely on the effectiveness of the collapse, and this fact is borne out by nearly all the published results of subsequent workers. Pleural adhesions are, of course, the outstanding cause of failure, but, in a small proportion of cases, the lung fails to collapse even when all adhesions have been divided by intrapleural pneumolysis. More than 95 per cent. of the cases in this series had evidence of pleural adhesions, and in those cases which had some degree of collapse the probability of success varied in inverse proportion to the extent of the adhesions. Thus, of those patients who showed evidence of adhesions over the upper and middle zone of the collapsed lung, rather less than half were classified as S.C. Of those patients who showed adhesions over the upper zone only, more than two-thirds were classified as S.C. Two conclusions are obvious—artificial pneumothorax must be commenced before adhesions are numerous (see Table V), and everything possible

should be done to improve the collapse by internal pneumolysis or paralysis of the phrenic nerve, or by combining these methods. In exceptional cases apical thoracoplasty combined with pneumothorax gives good results. It also appears that a bad, contraselective pneumothorax is worse than no pneumothorax at all, and it is very rarely desirable to continue an artificial pneumothorax when the cavity or cavities in the diseased lung fail to collapse. What may be described as the Micawber attitude, waiting for something to turn up, is too common. Usually what turns up in such cases is a severe pleural reaction, a spread of disease in the other lung, or a failure of the patient's strength and nutrition. A pneumothorax is either beneficial or harmful, and if a bad pneumothorax is stopped in time the life of the patient may be saved by other methods of treatment.

#### *Complications of Artificial Pneumothorax.*

Apart from the occurrence of a simple pleural effusion, or a benign tuberculous empyema complicating the artificial pneumothorax, 11 patients developed some serious complication as a result of the induction of artificial pneumothorax.

There were three cases of pyopneumothorax with secondary infection; two of these died within a year of the onset of the pyopneumothorax, while the third is in good health twelve years later.

There were five cases of spontaneous pneumothorax with secondary infection of the pleural cavity, occurring as a result of the tearing of pleural adhesions. Three of these died soon after the accident, the remaining two are now in good health. The two patients who recovered were treated by thoracoplasty.

One case of spontaneous pneumothorax died two weeks after the accident with no evidence of empyema.

One patient died of sudden cardiac failure.

One patient died of a spontaneous pneumothorax complicating a bilateral artificial pneumothorax.

The mortality from complications directly resulting from the treatment in these 400 patients was 2 per cent.

Simple pleural effusions or benign tuberculous empyemata occurred frequently in the series. It is not possible to draw a sharp line between a simple effusion and a tuberculous empyema in artificial pneumothorax cases. The fluid tends to become cloudy if it persists for a long time, and generally contains more tubercle bacilli than the 'idiopathic' pleural effusion which may precede phthisis. The presence of fluid was noted in 59 per cent. of the cases with some degree of collapse, but in 12 per cent. only a trace was present. In 9 per cent. of the cases with fluid a febrile reaction for more than two weeks coincided with the onset of the effusion. In 12 per cent. of the cases with effusion it was necessary to aspirate the fluid once or several times.

*Summary.*

1. Artificial pneumothorax was attempted in 400 patients and a satisfactory collapse was obtained in 131 patients (33 per cent.); it was not possible to obtain any collapse in 85 patients (21 per cent.); in 184 patients (46 per cent.) some degree of collapse was obtained, but the diseased areas of lung were not well collapsed.

2. The patients with satisfactory collapse showed a low mortality rate after five years, and even after a longer period. The great majority of the patients who are alive are in good health.

3. The patients with an unsatisfactory collapse showed a heavy mortality rate five years later. A small number of them are alive and well eight to thirteen years later.

4. The patients in whom it was impossible to induce an artificial pneumothorax showed a heavy mortality rate after five years, but fared rather better than those with an unsatisfactory collapse.

5. There is evidence that phrenic evulsion has contributed to lowering the mortality in all the groups, particularly those with an unsatisfactory collapse or no collapse.

6. The good results of artificial pneumothorax were almost entirely limited to those cases in which a good collapse was obtained. It appears that artificial pneumothorax should be stopped without delay as soon as it appears improbable that a good collapse is attainable.

7. Internal pneumolysis, phrenic evulsion, and phrenic crushing are most valuable methods of improving the collapse by artificial pneumothorax of a tuberculous lung.

8. Artificial pneumothorax was successful in 55 per cent. of cases induced within six months of the onset of illness; in 28 per cent. of cases induced six to twelve months after the onset; and in 20 per cent. of cases attempted more than twelve months after the onset.

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